Hindawi
Andrologia
Volume 2024, Article ID 3923652, 9 pages
https://doi.org/10.1155/2024/3923652

Research Article

Male Hyperuricemia Is Associated with Poor Reproductive Outcomes of IVF-ET

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Received 15 February 2023; Revised 29 June 2023; Accepted 26 December 2023; Published 16 January 2024

Academic Editor: Takashi Yazawa

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Objective. To investigate the effect of male hyperuricemia on reproductive outcome of in vitro fertilization-embryo transfer (IVF-ET). *Methods*. Clinical data of 412 couples who underwent their first cycle of IVF-ET were analyzed. According to the serum uric acid (SUA) level of the male, they were divided into control group (SUA $\leq 416\,\mu$mol/L) and hyperuricemia group (SUA $> 416\,\mu$mol/L). The primary and secondary observation indices were pregnancy outcome after quality fresh embryo transfer and embryo outcome after IVF. Binary logistic regression was used to analyze the relationship between male SUA and related pregnancy outcomes. The ROC curve of the effect of male SUA on biochemical pregnancy loss rate (BPLR) after fresh embryo transplantation was drawn. *Results*. BPLR in hyperuricemia group increased significantly than that in control group (4.7% vs. 31.6%, $P = 0.012$), and the clinical pregnancy rate and live birth rate were significantly lower (61.5% vs. 39.4%, $P = 0.038$) (56.9% vs. 33.3%, $P = 0.027$). Binary logistic regression analysis showed that BPLR after fresh embryo transfer was positively correlated with male SUA ($B = 0.010$, $P = 0.019$, OR = 1.010, 95% CI (1.002, 1.018)). The area under receiver operating characteristic curve was 0.784, the specificity was 53.7%, and the sensitivity was 100.0%, $P = 0.010$. Moreover, the total fertilization rate and 2PN fertilization rate in hyperuricemia group were significantly lower than those in control group (86.0% vs. 81.6%, $P = 0.001$) (75.0% vs. 69.6%, $P < 0.001$). *Conclusion*. Male hyperuricemia is an independent risk factor for increasing BPLR after fresh embryo transfer and can also reduce the total fertilization rate and 2PN fertilization rate of IVF.

1. Introduction

Uric acid (UA) is the final metabolite of purine nucleotides and has dual biological characteristics [1]. At normal levels, UA is the most abundant antioxidant in the human body, while high levels of serum uric acid (SUA) can participate in the occurrence of diseases. In addition to gout, SUA levels are also related to cardiovascular and cerebrovascular diseases [2–4], type 2 diabetes [5, 6], metabolic syndrome [7], and kidney diseases [8].

Hyperuricemia (HUA) refers to a fasting SUA concentration exceeding 416 μmol/L under a normal purine diet [9, 10]. Currently, with the improvement of the economy and living standards, the incidence of HUA is gradually increasing, affecting more males than females and developing at younger ages. Young males aged 20–29 years have the highest prevalence of HUA, with a rate as high as 31.9% [11]. A recent study found that HUA may reduce male semen quality and affect male fertility through oxidative stress and decreased testosterone levels [12]. However, the current literature has not investigated the relationship between male HUA and reproductive outcomes, and it is not clear whether male HUA affects embryo outcomes and pregnancy outcomes after fresh embryo transfer in couples undergoing in vitro fertilization-embryo transfer (IVF-ET), which is the problem that was explored in this study. Our primary observation index was pregnancy outcome after quality fresh embryo transfer, and the secondary observation index was embryo outcome after in vitro fertilization. The information described above is helpful in judging whether UA reduction interventions are

needed for men with HUA and fertility requirements and provides a basis for clinical treatment.

2. Materials and Methods

2.1. Patients. A retrospective cohort study was conducted to analyze the clinical data of 412 couples who underwent IVF-ET in the first cycle in the Reproductive Medicine Center of Affiliated Hospital of Nantong University from July 2017 to December 2021.

2.2. Inclusion Criteria. (1) Couples in which the woman's infertility was mainly caused by fallopian tube factors, aged 20−40 years old, and received ovulation induction therapy of antagonist regimen or short and long regimen. (2) The age of the male partner is 20−45 years old.

2.3. Exclusion Criteria. (1) Couples in which the male had obstructive azoospermia, nonobstructive azoospermia, or chromosome abnormality; (2) couples in which the male develops symptoms of gout, kidney, or eye lesions, and takes oral medication for treatment; and (3) couples in which the female had polycystic ovary syndrome (PCOS), abnormal ovulation, ovarian dysfunction or premature ovarian failure, chromosome abnormality, recurrent abortion, and uterine malformation like double uterus, mediastinal uterus, and unicorn uterus.

This project was approved by the Ethics Committee of the Affiliated Hospital of Nantong University. The requirement for written informed consent was waived due to the retrospective nature of this study.

2.4. Definition of Study Groups. The subjects were divided into two groups according to the man's SUA level: the control group (CG, SUA $\leq 416\,\mu$mol/L) and the hyperuricemia group (HG, SUA $> 416\,\mu$mol/L).

2.5. Clinical Protocols. Semen samples were collected by masturbation after 2–7 days of abstinence, and each sample was incubated at 37°C for a maximum of 60 min. After liquefaction, conventional semen analysis (sperm concentration and motility) was conducted according to the World Health Organization guidelines [13].

Venous blood samples were taken from every female patient on the second to third day of menstruation to assess the basic sex hormones, including follicle-stimulating hormone (FSH), luteinizing hormone (LH), progesterone (P), estradiol (E2), prolactin (PRL), and testosterone (T). The antral follicle count (AFC) in both ovaries was counted by transvaginal ultrasound, and the AFC statistics were completed by two experienced fertility doctors.

The ovulation induction protocol was the antagonist regimen [14] or the short-acting long-term regimen [15, 16]. LH, P, and E2 levels were evaluated continuously during ovulation induction, and follicular development and endometrial growth were monitored by transvaginal ultrasound. Once there were two or more dominant follicles with an average diameter greater than or equal to 17∼20 mm, 10,000 U of human chorionic gonadotropin (hCG, Shanghai Lizhu Pharmaceutical Co., Ltd.) or 250 μg of recombinant hCG (Aize, Merck Seronol, Switzerland) was injected that night; 36−38 hr after the follicles finally matured, the ova were extracted through the vagina under the guidance of transvaginal ultrasound. The extracted ova were washed with gamete buffer and transferred to fertilization culture medium for fertilization.

Oocytes were fertilized in a standard routine way [17]. From 16 to 18 hr after fertilization, the pronucleus was observed, and the appearance of double pronucleus (2PN) was considered normal fertilization. 2PN fertilized embryos were further cultured in embryo culture medium, and well-developed embryos that divided into four cells were evaluated the next day and showed normal cleavage. On the third day, the fertilized embryos divided into 6–9 blastomeres, with a uniform cell size, no granules in the cytoplasm, and a fragmentation rate of 0%–15% or a slightly uneven cell size, a few granules in the cytoplasm, and a fragmentation rate of 6%–20%; these embryos were regarded as day3 (D3) high-quality embryos [18], which were selected by the embryo cultivator for transplantation or freezing, and other well-developed embryos were taken for blastocyst culture. D3 high-quality cleavage embryos or high-quality blastocysts could be selected for fresh embryo transfer in the same cycle according to the physical and mental condition of the woman and the patients' wishes.

From the day of fresh embryo transfer, 200 mg/day progesterone soft capsules (Angeltan, BESINS) and 20 mg/day oral dydrogesterone (Abbott Biologics B.V.) were used for corpus luteum support. The serum hCG value was measured 10 days after embryo transfer. Patients with a normal increase in hCG were examined by transvaginal ultrasound ∼30 days after embryo transfer, and a detected original fetal heartbeat was judged as a clinical pregnancy; for these patients, luteal support continued until 70 days and gradually decreased until 90 days after pregnancy. Close attention was continuously paid to clinical pregnancies until delivery.

2.6. Definition of Relevant Results. The obtained oocytes are divided into germinal vesicle phase, meiosis metaphase I (M I), meiosis metaphase II (M II) according to their maturity, and MII was mature oocytes. hCG positive is defined as blood hCG value $\geq$10 mIU/mL, 10 days after embryo transfer. Biochemical pregnancy loss (BPL) refers to hCG positive in blood, but no gestational sac is found in intrauterine or extrauterine, and hCG level drops rapidly. Clinical pregnancy means gestational sac and the original fetal heartbeat can be detected in uterine cavity by transvaginal ultrasound at about 30 days after embryo transfer. Abortion refers to pregnancy failure after at least one intrauterine gestational sac or fetus was observed on ultrasound before 28 weeks of gestation. Live birth is defined as a newborn born alive at or after 28 weeks of gestation.

2.7. Interpretation of Clinical Indicators. Embryologic outcomes: total fertilization rate (total number of fertilized oocytes/number of oocytes used for fertilization $\times$ 100%), 2PN fertilization rate (two pronuclei number/number of oocytes used for fertilization $\times$ 100%), normal cleavage rate (normal cleavage number/two pronuclei number $\times$ 100%),

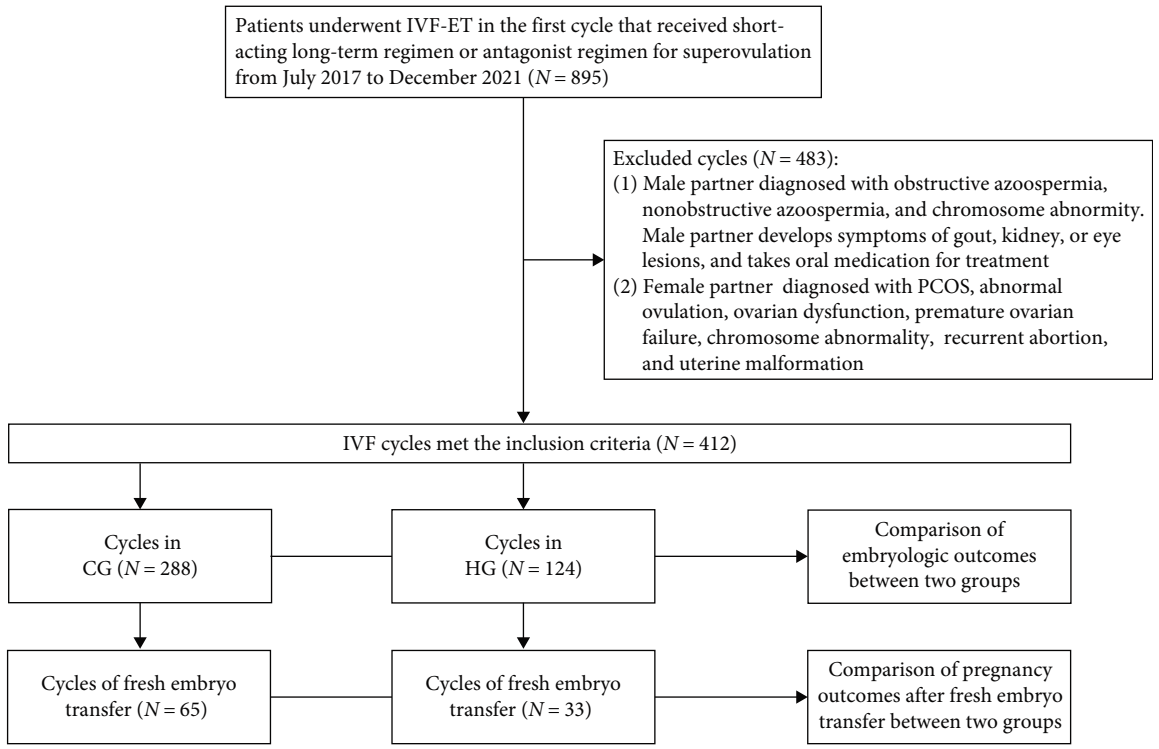

Figure 1: Flowchart of inclusion criteria and exclusion criteria. PCOS, polycystic ovary syndrome; CG, control group; and HG, hyperuricemia group.

and D3 high-quality embryos rate (number of D3 high-quality embryos/normal cleavage number × 100%).

Pregnancy outcomes: hCG-positive rate (number of hCG positive cycles/number of fresh embryo transfer cycles × 100%), biochemical pregnancy loss rate (BPLR, number of BPL cycles/number of hCG positive cycles × 100%), clinical pregnancy rate (number of pregnancy cycles/number of fresh embryo transfer cycles × 100%), abortion rate (number of abortion cycles before 28 weeks/number of clinical pregnancy cycles × 100%), and live birth rate (number of cycles with live birth/number of fresh embryo transfer cycles × 100%).

2.8. Statistical Analysis. SPSS 26.0 software was used for statistical analysis. The measurement data conforming to normal distribution were expressed by the mean ± standard deviation ($\overline{x} \pm$ SD), and the comparison between groups was carried out by independent sample *t*-test. The measurement data of non-normal distribution were expressed by median + quartile distance, and Mann–Whitney *U*-test was used for comparison between groups. The counting data were expressed by rate, and the comparison between groups was carried out by χ^2-test, continuity correction χ^2-test, or Fisher test. Binary logistic regression was used to analyze the relationship between male SUA and related pregnancy outcomes. The receiver operating characteristic (ROC) curve of the effect of male SUA on BPLR after fresh embryo transplantation was drawn. $P < 0.05$ was statistically significant.

3. Results

The process of inclusion and exclusion is shown in Figure 1. A total of 412 IVF cycles met the inclusion criteria, of which 288 cycles in the CG (accounting for 69.9%, SUA = 336.20 ± 48.57 μmol/L) had 65 fresh embryo transfer cycles, and 124 cycles in the HG (accounting for 30.1%, SUA = 480.10 ± 64.16 μmol/L) had 33 fresh embryo transfer cycles. The pregnancy outcome after fresh embryo transfer and the embryo outcome of in vitro fertilization were compared between the two groups.

3.1. Comparison of Baseline Characteristics of Female and Male Partners between Two Groups in the Fresh Embryo Transfer Cycles. A total of 98 quality fresh embryo transfer cycles in both groups, of which 65 were in the CG (male SUA = 340.95 ± 46.93 μmol/L) and 33 in the HG (male SUA = 480.18 ± 68.54 μmol/L). There was no significant difference in the baseline characteristics of the females between the two groups ($P > 0.05$). The semen volume of HG was significantly lower than that of CG (3.22 ± 1.34 ml vs. 2.60 ± 1.15 mL, $P = 0.025$), and there was no significant difference in the other baseline characteristics of male ($P > 0.05$), as shown in Table 1.

3.2. Comparison of Pregnancy Outcomes between Two Groups in the Fresh Embryo Transfer Cycles. After quality fresh embryo transfer, there was one ectopic pregnancy in the CG. Compared with the CG, in the HG, the BPLR visibly

Table 1: Baseline characteristic of female and male partners between two groups in the fresh embryo transfer cycles.

	CG ($N=65$)	HG ($N=33$)	$\chi^2/t/Z$	P
Female				
Age (year)	29.28 ± 3.60	30.09 ± 3.70	−1.047	0.298
BMI (kg/m^2)	22.21 ± 3.65	22.38 ± 3.09	−0.230	0.819
Infertility duration (year)	2 (1, 3)	2 (1, 3)	−0.746	0.456
Infertility type (case (%))	—	—	0.006	0.941
Primary infertility	34/65 (52.3)	17/33 (51.5)	—	—
Secondary infertility	31/65 (47.7)	16/33 (48.5)	—	—
Basic FSH (mIU/mL)	6.86 ± 1.56	7.44 ± 2.04	−1.554	0.123
Basic LH (mIU/m)	4.38 (2.87, 5.58)	4.63 (3.10, 6.55)	−0.752	0.452
Basic E2 (pg/mL)	45.39 ± 14.84	45.49 ± 18.93	−0.028	0.978
AFC (n)	11 (8, 15)	10 (7, 14)	−1.453	0.146
Ovulation induction (case (%))	—	—	2.188	0.139
Short-acting long-term regimen	21/65 (32.3)	6/33 (18.2)	—	—
Antagonist regimen	44/65 (67.7)	27/33 (81.8)	—	—
Gn used dosage (U)	1687.5(1,462.5, 2,025.0)	1,575.0 (1,350.0, 1,912.5)	−0.864	0.388
Gn used duration (day)	8 (7, 9)	7 (7, 8)	−1.319	0.187
Average E2 level of follicles with diameter ≥14 mm on hCG trigger day (pg/mL)	254.73 (195.58, 389.63)	255.31 (193.23, 330.09)	−0.274	0.784
Endometrial thickness on hCG trigger day (mm)	10.45 (9.40, 12.07)	11.00 (9.83, 12.40)	−1.027	0.305
Endometrial classification on hCG trigger day (case (%))$^{\#}$	—	—	0.121	0.728
A	60/65 (92.3)	29/33 (87.9)	—	—
B	5/65 (7.7)	4/33 (12.1)	—	—
Number of retrieved oocytes (n)	9.26 ± 2.91	8.42 ± 3.75	1.218	0.226
Number of MII stage oocyte (n)	7 (5, 8)	6 (4, 8)	−0.333	0.739
MII stage oocyte rate (%)	70.0 (57.9, 100.0)	76.2 (54.78, 100.0)	−0.633	0.527
Number of oocytes used for fertilization (n)	9.11 ± 2.97	8.18 ± 3.78	1.328	0.187
Proportion of fresh embryo transfer cycle (case (%))	65 (22.6)	33 (26.6)	0.782	0.377
D3 embryos/blastocyst transfer ratio (case)	45/20	24/9	0.128	0.720
Number of embryos transferred (n)	1.52 ± 0.50	1.39 ± 0.50	1.206	0.231
Male				
Age (year)	30.52 ± 4.33	30.00 ± 4.23	0.569	0.571
BMI (kg/m^2)	24.17 ± 3.13	24.95 ± 2.32	−1.271	0.207
Infertility type (case (%))	—	—	0.414	0.520
Primary infertility	39/65 (60.0)	22/33 (66.7)	—	—
Secondary infertility	26/65 (40.0)	11/33 (33.3)	—	—
Semen analysis	—	—	—	—
Semen volume (mL)	3.22 ± 1.34	2.60 ± 1.15	2.279	0.025*
Sperm concentration (10^6/mL)	84.29 ± 61.58	85.50 ± 63.62	−0.091	0.928
Total sperm motility (%)	52.23 ± 17.05	48.09 ± 23.07	1.005	0.317
Progressive motility (%)	41.17 ± 14.50	37.96 ± 18.61	0.938	0.351
Total sperm count (10^6)	249.08 ± 171.59	229.10 ± 200.01	0.515	0.608

BMI, body mass index; CG, control group; HG, hyperuricemia group. *$P < 0.05$. $^{\#}$Continuity correction χ^2-test.

increased (4.7% vs. 31.6%, $P = 0.004$), and the clinical pregnancy rate and live birth rate significantly decreased (61.5% vs. 39.4%, $P = 0.038$) (56.9% vs. 33.3%, $P = 0.027$). There was no significant difference in the hCG-positive rate or abortion rate between the two groups ($P > 0.05$), as shown in Table 2.

3.3. Binary Logistic Regression Analysis of Male SUA and Related Pregnancy Outcomes. Binary logistic regression was used to analyze the relationship between male SUA and BPLR, clinical pregnancy rate, and live birth rate after fresh embryo transfer. The results showed that there was a positive correlation between the male SUA and the BPLR after fresh

Table 2: Comparison of pregnancy outcomes between two groups in the fresh embryo transfer cycles.

	CG ($N=65$)	HG ($N=33$)	χ^2	P
hCG positive rate (case (%))	43/65 (66.2)	19/33 (57.6)	0.693	0.405
BPLR (case (%))[#]	2/43 (4.7)	6/19 (31.6)	6.275	0.012*
Clinical pregnancy rate (case (%))	40/65 (61.5)	13/33 (39.4)	4.322	0.038*
Abortion rate (n/N (%))[#]	3/40 (7.5)	2/13 (15.4)	0.089	0.765
Live birth rate (case (%))	37/65 (56.9)	11/33 (33.3)	4.874	0.027*

BPLR, biochemical pregnancy loss rate; CG, control group; HG, hyperuricemia group. *$P<0.05$. [#]Continuity correction χ^2-test.

Table 3: Binary logistic regression analysis of male SUA and related pregnancy outcomes.

	B	SE	Wald χ^2	P	OR	95% CI
BPLR (case (%))	0.010	0.004	5.535	0.019*	1.010	(1.002, 1.018)
Clinical pregnancy rate (case (%))	−0.004	0.002	2.724	0.099	0.996	(0.991, 1.001)
Live birth rate (case (%))	−0.004	0.003	3.109	0.078	0.996	(0.991, 1.000)

BPLR, biochemical pregnancy loss rate; B, regression coefficient B; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval. *$P<0.05$.

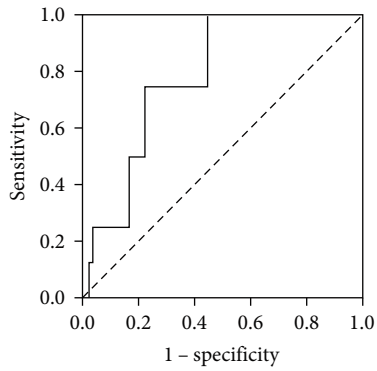

Figure 2: ROC curve of effect of male SUA on BPLR after fresh embryo transfer. ROC, receiver operating characteristic.

embryo transfer ($B=0.010$, $P=0.019$, OR = 1.010, 95% CI (1.002, 1.018). BPLR increased by 1% for every 1 μmol/L increase in male SUA. The male SUA had no significant effect on the clinical pregnancy rate and live birth rate after fresh embryo transfer ($P>0.05$), as shown in Table 3.

3.4. ROC Curve of Effect of Male SUA on BPLR after Fresh Embryo Transfer. According to the BPLR in hCG positive patients, the ROC curve of male SUA predicting BPLR after fresh embryo transfer was drawn. The results showed that the area under the curve was 0.784, the cleavage value of male SUA was 369 μmol/L, the specificity was 53.7%, the sensitivity was 100.0%, $P=0.010$, as shown in Figure 2.

3.5. Comparison of Baseline Characteristics of Female and Male Partners between Two Groups in IVF Cycles. A total of 412 IVF cycles in both groups, of which 288 were in the CG (male SUA = 335.98 ± 48.96 μmol/L) and 124 in the HG (male SUA = 481.19 ± 64.11 μmol/L). There was no significant difference in the baseline characteristics of the females between the two groups ($P>0.05$). The body mass index (BMI) of the male patients was higher (24.19 ± 3.50 vs. 25.82 ± 4.08, $P<0.001$), and the age was lower in the HG than in the CG (30.89 ± 4.64 vs. 29.54 ± 3.51, $P=0.002$). The semen volume (3.09 ± 1.42 mL vs. 2.65 ± 1.17 mL, $P<0.001$), sperm concentration (84.32 ± 56.46 vs. 72.26 ± 49.21, $P=0.040$), total sperm motility (51.47 ± 18.35 vs. 46.56 ± 20.32, $P=0.016$), and total sperm count (236.13 ± 168.79 vs. 191.71 ± 156.60, $P=0.013$) of the HG were significantly lower than those of the CG, as shown in Table 4.

3.6. Comparison of Embryo Outcomes between Two Groups in IVF Cycles. The total fertilization rate and 2PN fertilization rate in the HG were significantly lower than those in the CG (86.0% vs. 81.6%, $P=0.001$) (75.0% vs. 69.6%, $P<0.001$). There was no significant difference in the normal cleavage rate or D3 high-quality embryo rate between the two groups ($P>0.05$), as shown in Table 5.

4. Discussion

With the economical development, the diet of Chinese people has changed from a diet structure dominated by plant fiber to a diet of high fat, high salt, and high protein, resulting in a higher prevalence of HUA in the population at the peak of fertility. Therefore, in recent years, the influence of abnormal UA metabolism on reproduction has attracted great attention. In June 2022, Mu et al. [19], after studying 1,032 infertile women with PCOS in the first IVF or intracytoplasmic sperm injection cycle, suggested that the increase in SUA was related to decreased live birth rate, hCG positive rate, clinical pregnancy rate, and increased miscarriage rate in PCOS women. At present, young men have the highest prevalence of hyperuricemia [11]; however, the abnormal SUA level in men is often ignored during assisted reproductive therapy, and the influence of male HUA on pregnancy outcomes has not been reported. Therefore, this study has considerable clinical significance. More than 30% of male IVF-treated patients suffer from HUA. Male hyperuricemia, according to our study, is an independent risk factor for

Table 4: Comparison of baseline characteristics of female and male partners between two groups in IVF cycles.

	CG ($N=288$)	HG ($N=124$)	$\chi^2/t/Z$	P
Female				
Age (year)	29.32 ± 3.54	29.60 ± 3.32	−0.753	0.452
BMI (kg/m^2)	22.51 ± 3.54	22.67 ± 5.55	−0.333	0.739
Infertility duration (year)	2 (1, 3)	3 (2, 4)	−1.375	0.169
Infertility type (case (%))	—	—	0.287	0.592
Primary infertility	152/288 (52.8)	69/124 (55.6)	—	—
Secondary infertility	8,136/288 (47.2)	55/124 (44.4)	—	—
Basic FSH (mIU/mL)	6.98 (5.90, 8.13)	7.04 (6.08, 8.09)	−0.359	0.719
Basic LH (mIU/mL)	4.12 (3.22, 5.46)	4.42 (3.13, 5.98)	−0.255	0.799
Basic E2 (pg/mL)	43.00 (34.00, 54.88)	43.97 (34.34, 55.00)	−1.599	0.110
AFC (n)	10 (8, 15)	10 (8, 14)	−0.102	0.919
Ovulation induction (case (%))	—	—	1.382	0.240
Short-acting long-term regimen	65/288 (22.9)	22/124 (17.70)	—	—
Antagonist regimen	222/288 (77.1)	102/124 (82.3)	—	—
Gn used dosage (U)	1,725.00 (1,500.00, 2,025.00)	1,725.00 (1,575.00, 1,950.00)	−0.790	0.429
Gn used duration (day)	8 (7, 9)	8 (7, 8)	−0.368	0.713
LH levels on hCG trigger day (mIU/mL)	2.26 (1.55, 4.11)	2.80 (1.55, 4.66)	−1.388	0.165
P levels on hCG trigger day (ng/mL)	1.19 (0.86, 1.48)	0.99 (0.81, 1.48)	−1.777	0.075
E2 levels on hCG trigger day (pg/mL)	2,640.00 (1,878.00, 4,201.00)	2,492.00 (1,643.36, 4,275.00)	−1.039	0.299
Average E2 level of follicles with diameter ≥14 mm on hCG trigger day (pg/mL)	408.77 (297.06, 575.08)	388.89 (254.67, 570.65)	−1.731	0.083
Number of retrieved oocytes (n)	9 (6, 12)	9 (6, 12)	−0.436	0.663
Number of MII stage oocyte (n)	6 (4, 8)	6 (4, 8)	−0.692	0.489
MII stage oocyte rate (%)	62.5 (55.6, 75.0)	60.0 (53.8, 100.0)	−0.129	0.897
Number of oocytes used for fertilization (n)	9 (6, 12)	9 (6, 12)	−0.311	0.756
Male				
Age (year)	30.86 ± 4.63	29.55 ± 3.53	2.814	0.005
BMI (kg/m^2)	24.22 ± 3.49	25.82 ± 4.09	−4.052	<0.001***
Infertility type (case (%))	—	—	1.912	0.167
Primary infertility	172/288 (59.7)	83/124 (66.9)	—	—
Secondary infertility	116/288 (40.3)	41/124 (33.1)	—	—
Semen analysis	—	—	—	—
Semen volume (mL)	3.09 ± 1.42	2.65 ± 1.17	3.217	0.001**
Sperm concentration (10^6/mL)	84.32 ± 56.46	72.26 ± 49.21	2.065	0.040*
Total sperm motility (%)	51.47 ± 18.35	46.56 ± 20.32	2.412	0.016*
Progressive motility (%)	40.37 ± 15.56	37.53 ± 16.71	1.658	0.098
Total sperm count (10^6)	236.13 ± 168.79	191.71 ± 156.60	2.503	0.013*

BMI, body mass index; CG, control group; HG, hyperuricemia group. *$P<0.05$, **$P<0.01$, ***$P<0.001$.

increasing BPLR after fresh embryo transfer and can also reduce the total fertilization rate and 2PN fertilization rate of in vitro fertilization, which is associated with poor reproductive outcomes of IVF-ET.

IVF-ET is a routine assisted reproductive technology for infertile couples, whose most urgent wish is to have a baby. However, we find that after transferring quality fresh embryos, the BPLR in the hyperuricemia group increases more than seven times than that of the control group (up to 31.6%), eventually leading to a decrease in clinical pregnancy rate and live birth rate. BPL is an early pregnancy loss characterized by a gestational sac that forms and grows when an embryo fails to develop, greatly influencing the pregnancy outcome of IVF treatment. However, the BPL etiology is still unclear. The main hypothesis is that BPL is related to poor embryo quality or impaired endometrial receptivity. Some studies also reveal that BPL is linked to female age, embryonic development stage, or abnormal chromosome structure. However, more and more studies describe that BPL is not related to female age [20, 21], endometrial abnormality [22, 23], or chromosome structure abnormality [21, 23]; instead, poor embryo quality dose increases BPLR [24].

Table 5: Comparison of embryo outcomes between two groups in IVF cycles.

	CG ($N=288$)	HG ($N=124$)	χ^2	P
Total fertilization rate (n (%))	2,246/2,613 (86.0)	943/1,156 (81.6)	11.811	0.001**
2PN fertilization rate (n (%))	1,960/2,613 (75.0)	804/1,156 (69.6)	12.215	<0.001***
Normal cleavage rate (n (%))	1,946/1,960 (99.3)	798/804 (99.3)	0.008	0.928
D3 high-quality embryo rate (n (%))	1,259/1,946 (64.7)	519/798 (65.0)	0.029	0.865

CG, control group; HG, hyperuricemia group. **$P<0.01$, ***$P<0.001$.

Few studies have reported the increase in BPL caused by male factors. However, the main factor in men affecting embryo quality is lower sperm quality, and the most fully studied one is the damage of oxidative stress to sperm. Oxidative stress in seminal plasma can increase the sperm DNA fragmentation index (DFI), chromatin crosslinking, and abnormal base modification, reduce sperm DNA integrity, and change sperm structure and function [25–27]. Simon et al. [28], through a met analysis, showed that the increase in sperm DFI is related to a significantly reduced clinical pregnancy rate. Lee et al. [29] proposed a significant negative correlation between sperm DFI and embryo quality. Other studies have shown that the differential expression of sperm noncoding RNA [30], sperm histone modification, and sperm DNA methylation [31] affected sperm and embryo quality. UA is an antioxidant in seminal plasma [32], while the UA content in the seminal plasma of infertile men with HUA decreases significantly [12]. Hughes et al. [33] reported that adding 400 μM UA to seminal plasma in vitro under X-ray irradiation could significantly reduce the sperm DFI and prevent sperm DNA damage. UA, as an antioxidant in seminal plasma, maintains sperm DNA integrity. However, the effect of HUA on sperm DFI is still unknown. Ma et al. [34] determined differentially expressed miRNAs in the testicular tissue of HUA rats; however, their effects on sperm quality were not further explored. It is unclear whether HUA can reduce embryo quality by increasing sperm DFI or changing the expression of sperm noncoding RNA, which needs to be further explored. Our study suggests that male HUA reduces embryo quality, affects the development of earliest embryos in the uterine cavity, and increases adverse pregnancy outcomes. Male HUA is an independent risk factor for BPL after fresh embryo transplantation and may be used as a predictive factor, and the cut-off value was SUA 369 μmol/L, which suggests that for men with fertility requirements, SUA exceeding 369 may indicate adverse reproductive outcomes and require treatment.

We also explore the effect of male HUA on the embryo outcome after IVF, finding that male HUA can reduce the success rate of conventional in vitro fertilization. Normal fertilization is the key to the success of IVF. Canceling the IVF treatment cycle in the clinic is also common due to fertilization failure. Among the existing databases, it is rare to directly study the influence of male HUA on conventional in vitro fertilization. Ma et al. [12] reported that a higher level of SUA in men could affect the secretion of epididymis by oxidative stress and reduce semen volume and sperm count. The UA content in the seminal plasma of infertile men with HUA decreases significantly [12]; while UA is an antioxidant in seminal plasma [32]; thus, the increased oxidative stress in HUA male seminal plasma can cause mitochondrial dysfunction and germ cell apoptosis, reducing sperm density and motility [35]. In addition, the secretion of sex hormones is disordered in men with HUA; thus, they have reduced levels of testosterone and estradiol. It has been reported in previous studies that HUA leads to male hypogonadism [36]. Elevated SUA levels can also reduce the NO content and activity in blood vessels, causing erectile dysfunction [37, 38]. These researches indicate that HUA can reduce the semen volume, sperm concentration, total sperm count, and sperm motility of male through various mechanisms. These are consistent with our research results, and the semen volume, sperm concentration, total sperm count, and sperm motility of males in HG significantly decreased. In male semen, the total number of forward motility sperm is the most critical index affecting fertilization [39]. HUA reduces semen quality by affecting the secretion of epididymis, reduces the rate of conventional in vitro fertilization, and decreases the number of transferable embryos during IVF.

In our study, male HUA barely affects the fertilized egg division in vitro, and the formation rate of D3 high-quality embryos in the two groups is similar. We believe that this may be due to the development of IVF therapy and the improvement of embryo culture system, which improves the adverse effects of HUA on sperms, so there was no significant difference between embryo outcomes.

Our study is the first to investigate the influence of male HUA on the reproductive pregnancy outcomes of IVF-ET. The limitation of this study lies in the small number of fresh embryo transfer cycles, retrospective nature, and the mechanism of BPLs could not be discovered. In the future, we will further increase the number of clinical cases, conduct multicenter joint clinical studies, and explore the specific mechanism by which male HUA affects embryo development potential.

5. Conclusion

Our study preliminarily reveals that male HUA is associated with poor reproductive outcomes of IVF-ET, which is an independent risk factor for increasing BPLR after fresh embryo transfer, and can also reduce the total fertilization rate and 2PN fertilization rate of in vitro fertilization. Therefore, we suggest that attention should be given to the SUA level of men in clinical work, and education and UA reduction interventions need to be carried out in a timely manner for men with HUA who have fertility requirements to improve pregnancy outcomes for patients.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Authors' Contributions

Ying Wu designed this study and wrote the manuscript. Qian Gao and Jin-ran Li provided clinical data and corrected data. Xin Li provided analysis methods. Min Huang and Yuan-chen Yang analyzed data. Xiao-li Sun and Xu-hui Zeng edited the manuscript. All authors have read and approved the manuscript. Ying Wu, Qian Gao, and Jin-ran Li contributed equally to the work and should be regarded as co-first authors. Xiao-li Sun and Xu-hui Zeng contributed equally to the work and should be regarded as co-corresponding authors.

Acknowledgments

The authors acknowledge the invaluable contribution of the participants.

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