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The correlation between serum fructose levels and pregnancy outcomes in IVF patients with and without PCOS: a case-control study

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Abstract

Background Excessive fructose intake can impact pregnancy health. Additionally, Polycystic ovary syndrome (PCOS) is associated with both elevated fructose levels and adverse pregnancy outcomes. Therefore, it is significant to investigate whether serum fructose levels influence pregnancy outcomes in patients with or without PCOS.

Methods This case-control study included 270 participants (PCOS, $n=135$; non-PCOS, $n=135$). The serum fructose levels of consecutively treated women undergoing in vitro fertilization - embryo transfer treatment at the Center of reproductive medicine in Shengjing hospital of China Medical University, from June 2020 to June 2021, were measured. Pregnancies were monitored until the ultimate outcome was determined. The antenatal, delivery, and neonatal outcomes were extracted from hospital records.

Results In patients with PCOS, those who experienced miscarriage had significantly higher serum fructose levels ($P=0.011$). The incidence of miscarriage increased as the serum fructose quartiles increased in patients with PCOS ($P=0.010$). There was a significant correlation between serum fructose levels and miscarriage ($r=0.258$, $P=0.002$). The results of multivariate logistic regression analysis remain consistent (odd ratio [OR] = 10.138, $P=0.005$). Conversely, in women without PCOS, those who prematurely delivered had significantly higher serum fructose levels ($P=0.001$). The incidence of preterm delivery increased as the serum fructose quartiles increased in patients without PCOS ($P<0.001$). There was a significant correlation between serum fructose levels and preterm delivery ($r=0.311$, $P<0.001$) in non-PCOS group. The multivariate logistic regression analysis indicated the identical results (OR = 18.359, $P=0.008$). The area under the curve for fructose-mediated prediction of miscarriage in PCOS was 0.686, while for prediction of preterm birth in non-PCOS individuals, the area under the curve was 0.731.

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Conclusions Serum fructose levels are positively associated with miscarriage risk in patients with PCOS. Within the non-PCOS cohort, fructose levels are linked to preterm birth. Further investigation is warranted to comprehensively elucidate the underlying mechanisms, thus enhancing our profound understanding.

Keywords Fructose, Polycystic ovary syndrome, Miscarriage, Preterm birth, Pregnancy outcome

Background

Polycystic ovary syndrome (PCOS) is a prevalent clinical endocrine and metabolic dysfunction that impacts women of reproductive age, manifesting in clinical features such as menstrual irregularities, anovulation, and subfertility [1, 2]. PCOS is the most common cause of anovulatory infertility [3], affecting not only oocyte quality [4] but also endometrial function [5]. In China, the incidence of PCOS in women of childbearing age is approximately 5.6% [6]. Although many patients with PCOS can achieve conception following ovulation induction therapies, it is critical that these individuals face elevated risks of preterm birth, miscarriage, gestational diabetes mellitus and pregnancy-induced hypertension [7, 8]. Our previous investigation revealed elevated serum fructose levels in patients with PCOS compared to those without PCOS. Moreover, these elevated fructose levels were associated with metabolic imbalances within the PCOS cohort [9, 10].

Fructose, a monosaccharide extensively employed in food processing, has raised concerns owing to increased consumption and subsequent health implications. It undergoes hepatic metabolism [11], contributing to ATP depletion, thus facilitating lipid synthesis [12], and triggering oxidative stress [13]. Fructose and its metabolites, whether directly or indirectly, cause metabolic-related diseases, such as obesity and insulin resistance [14, 15]. Moreover, emerging research suggests a potential link between high fructose levels and adverse pregnancy health. Elevated serum fructose in early gestation has been correlated with an increased likelihood of gestational diabetes [16]. Saben et al. [17] reported that excessive maternal fructose intake reduced the pregnancy rates in mice and disrupted decidualization. Nevertheless, the correlation between serum fructose levels and pregnancy outcomes in patients with PCOS remains unclear.

Given the negative impact of PCOS on pregnancy and its connection with serum fructose levels, it is crucial to assess whether fructose exerts differential effects on pregnancy outcomes in patients with or without PCOS. Consequently, we conducted a case-control study aimed at investigating the influence of serum fructose levels on pregnancy outcomes in both PCOS and non-PCOS populations.

Methods

Study design and participants

A case-control study was designed to investigate the association between serum fructose levels and pregnancy outcomes in women with or without PCOS undergoing IVF/ICSI treatment. To avoid the impact of multiple pregnancies on pregnancy outcomes, we only included women with singleton pregnancies. We determined the required sample size using the ClinCalc Sample Size Calculator (available at https://clincalc.com/stats/samplesize.aspx). Given an effect size of 0.95, a type I error rate of 0.05, and a desired power of 80%, we calculated that 127 subjects per group would be needed. Therefore, 270 participants who were diagnosed with clinical pregnancy (PCOS, $n = 135$; Control, $n = 135$) following in vitro fertilization (IVF) - embryo transfer treatment with completed serum fructose level test from China Medical University's Center for Reproductive Medicine at Shengjing Hospital were chosen at random.

The exclusion criteria have been detailed in a prior publication [10, 18]. In brief, these criteria encompassed the following: a duration of less than three years since menarche; smoking; use of hormonal medications; pregnant; breastfeeding; the presence of endocrine disorders such as diabetes mellitus and androgen-secreting tumors; as well as a history of tumor, infectious, or inflammatory diseases; recent consumption of specific medications within the preceding six months, including oral contraceptives, aspirin, insulin-sensitizing drugs, corticosteroids, nicotinic acid, anti-androgens, gonadotropin-releasing hormone (GnRH) agonists and antagonists.

The Rotterdam criteria was used to diagnosed PCOS [19]. (1) Patients exhibit anovulation or reduced ovulatory frequency; (2) The presence of hyperandrogenism is established; (3) Polycystic ovarian morphology is confirmed by B-ultrasonography. Individuals meeting both aforementioned criteria are eligible for a PCOS diagnosis. Non-PCOS patients were included if they were diagnosed with infertility but did not meet the Rotterdam criteria for PCOS.

The basic information of the participants was obtained from the electronic medical record database, such as age and BMI (body mass index). Prior to their involvement in the study, all participants were granted an exemption of informed consent. This exemption was based on the removal of any identifying information from patient specimens and data, ensuring the complete safeguarding of patient privacy. The specimens employed in this

research were derived from discarded clinical samples post standard diagnostic and therapeutic procedures, thereby having no effect on the routine medical care and diagnosis of patients. Supplementary Table 1 provides an overview of participants' characteristics in this study. The protocol for ovulation stimulation and IVF is detailed in the Supplementary Flie.

Measurement of basic hormone levels

Every participant had venous blood samples collected in the natural menstrual cycle on days three through five after a minimum 12-hour fast. A 15-minute centrifugation at 3000 × g was then applied to the blood samples.

The quantification of following hormones in blood samples was conducted through chemiluminescence assays on the UniCel DxI 800 Automatic Immunoassay System (Beckman Coulter, USA), along with commercially available kits, following the protocols prescribed by the manufacturer and supplier. The hormones assessed included total testosterone (Total T) (C10160), follicle-stimulating hormone (FSH) (C10156), luteinizing hormone (LH) (C10155), progesterone (C10159), prolactin (C10158), estradiol (C10161), and anti-Müllerian hormone (AMH) (B13127). The corresponding reference ranges were < 0.35 ng/mL for Total T, 3.85–8.78 mIU/mL for FSH, 2.12–10.89 mIU/mL for LH, 0.31–1.52 ng/mL for progesterone, 3.34–26.72 ng/mL for prolactin, 15.16-148.13 pg/mL for estradiol, and 1.2–6.5 ng/mL for AMH. All these indicators were measured in the Department of Laboratory Medicine at Shengjing Hospital, and the reference ranges provided were established by the laboratory.

Additionally, the Enzyme-Linked Immunosorbent Assay was used to measure the levels of dehydroepiandrosterone sulfate (DHEAS) (CSB-E05105h, Cusabio Biotech, Wuhan, China), sex hormone-binding globulin (SHBG) (Human SHBG ELISA Kit; RayBiotech, Norcross, GA, USA), and free testosterone (CSB-E05096h, Cusabio Biotech, Wuhan, China). The minimum detectable concentrations for DHEAS, SHBG, and free testosterone are 10 ng/mL, 1.2 pmol/L, and 3.75 pg/mL, respectively. For DHEAS, SHBG and free testosterone, the corresponding intra-assay coefficients of variation (CVs) were 6.1%, 6.8% and 5.5%, while the inter-assay CVs were 9.2%, 10.2% and 8.3%. The optical density of each sample was compared to standard curves at 450 nm to estimate the final hormone levels.

Measurement of serum Fructose levels

Fructose concentrations were measured using a fructose fluorometric kit (K611-100; BioVision Incorporated, Milpitas, CA, USA). Each serum sample was diluted 1:2 in the supplied assay buffer before measurement. Subsequently, the assay was executed following the manufacturer's protocol. Enzymatic processing was applied to free fructose, resulting in the generation of metabolites that subsequently interacted with the fluorescent probe, yielding measurable fluorescence at Ex/Em wavelengths of 535/587 nm. To eliminate interference from glucose, a sample purification mix reagent was employed. The assay exhibited a dynamic range of 5-500 pmol/well, with intra-assay and inter-assay CVs recorded at 7.8% and 10.2%, respectively.

Statistical analysis

The Statistical Package for Social Sciences, version 22 (IBM Corp., Armonk, NY), was used for all statistical analyses. The Kolmogorov-Smirnov test was employed to determine if the continuous variables' distribution was normally distributed. Continuous variables with a normally distribution were reported as mean ± standard deviation, whereas those with a non-normally distribution were reported as median (interquartile range). Data confirmed to follow a normal distribution and demonstrated homogeneity of variances were then subjected to the student's t-test or analysis of variance for comparative analyses. Non-parametric tests including Mann–Whitney U test and the Kruskal-Wallis H test were used for other conditions. Chi-square test or Fisher's exact test were used to assess categorical variables, which were presented as percentages. The Spearman test was used to analyze the correlation. The correlation between serum fructose levels and pregnancy outcomes was further assessed using univariate and multivariate logistic regressions. The covariates influencing pregnancy outcomes were chosen using univariate logistic regression analysis, and the factors that the univariate analysis determined to be significant were included in the multivariate logistic regression analysis. Multivariate logistic regression analysis was used to adjust the interference of confounding factors, regarding the impact of fructose levels on pregnancy outcomes. Receiver operating characteristic (ROC) curves were used to assess the diagnostic performance of serum fructose levels in the pregnancy outcome of patients with or without PCOS, including evaluations of the area under the curve (AUC), sensitivity, specificity, positive predictive value, and negative predictive value. A significance level of $P < 0.05$ was used to all two-sided statistical tests.

Results

Significant difference in serum Fructose levels based on pregnancy outcomes

As revealed by Table 1, notable variation in serum fructose levels were observed across different pregnancy outcome categories in those with PCOS ($P = 0.011$) and those without PCOS ($P = 0.001$) groups. Particularly, among the PCOS cohort, the highest serum fructose level was

Table 1 Description of the study participants in term delivery, preterm delivery, and miscarriage groups

	Control ($n=135$)				PCOS ($n=135$)			
	Term delivery	**Preterm delivery**	**Miscarriage**	***P*-value**	**Term delivery**	**Preterm delivery**	**Miscarriage**	***P*-value**
N	84	25	26		81	27	27	
Serum fructose (pmol/μL)	8.38 (7.40–9.44)	10.25 (8.43–11.22)	8.35 (6.38–9.84)	0.001*	9.48 (8.05–11.33)	8.99 (7.51–10.76)	11.74 (8.59–15.25)	0.011*
Maternal age (y)	31.38 ± 0.472	32.76 ± 0.769	32.12 ± 0.726	0.328	30.00 (28.00–33.00)	31.00 (29.00–34.00)	30.00 (28.00–32.00)	0.344
Maternal BMI (kg/m^2)	25.60 (24.00–28.00)	25.00 (22.60-27.15)	26.10 (24.35–27.15)	0.277	25.42 ± 0.452	27.09 ± 0.799	26.10 ± 0.872	0.194
Type of infertility				0.799				0.758
Primary	43 (51.2%)	11 (44.0%)	13 (52.0%)		54 (66.7%)	20 (74.1%)	19 (70.4%)	
Secondary	41 (48.8%)	14 (56.0%)	12 (48.0%)		27 (33.3%)	7 (25.9%)	8 (29.6%)	
Basic hormone levels								
FSH (mIU/mL)	6.99 (5.61–8.16)	7.15 (5.97–8.45)	7.62 (6.29–8.45)	0.483	6.22 (5.48–7.76)	6.27 (5.47–7.36)	5.35 (4.86–6.87)	0.084
LH (mIU/mL)	3.97 (2.71–5.33)	3.97 (3.23–6.22)	3.03 (2.56–4.24)	0.125	7.44 (4.66–13.93)	7.72 (4.50-11.41)	7.14 (5.35–13.08)	0.947
Estradiol (pg/mL)	42.00 (32.50–56.50)	41.00 (30.00–44.00)	42.00 (34.50–49.00)	0.490	49.50 (40.00–64.00)	51.50 (41.50-79.25)	53.00 (38.00-67.32)	0.658
Progesterone (ng/mL)[a]	0.58 (0.41–0.88)	0.50 (0.31–0.69)	0.54 (0.38–0.86)	0.253	0.56 (0.35–0.85)	0.54 (0.43–0.89)	0.56 (0.37–0.98)	0.764
Total T (ng/mL)	0.52 (0.36–0.64)	0.53 (0.33–0.71)	0.52 (0.32–0.68)	0.976	0.62 (0.49–0.75)	0.63 (0.44–0.74)	0.69 (0.55–0.80)	0.219
Free T (nM)	0.02 (0.02–0.03)	0.02 (0.02–0.03)	0.03 (0.02–0.04)	0.124	0.03 (0.02–0.04)	0.03 (0.02–0.04)	0.03 (0.03–0.04)	0.245
SHBG (nM)	32.65 (23.75–43.03)	35.10 (21.30–51.70)	30.50 (19.05–43.38)	0.755	27.85 (14.48–41.58)	26.80 (18.50–30.40)	19.55 (12.35–23.93)	0.182
DHEAS (nM)	3390 (2285–4347)	3956 (2188–5753)	3347 (2274–4775)	0.670	3581 (2446–7188)	4153 (2726–6136)	5677 (3461–8351)	0.064
AMH (ng/mL)	3.05 (1.98–4.63)	3.54 (1.59–5.79)	3.20 (1.56–4.25)	0.922	7.80 (4.67–11.16)	8.53 (4.61–13.26)	9.35 (6.57–11.80)	0.305
Prolactin (ng/mL)	11.55 (9.05–15.43)	10.98 (9.14–13.24)	11.11 (8.60-18.12)	0.670	10.17 (7.82–13.80)	10.80 (6.45–15.98)	9.70 (7.09–11.93)	0.455
FAI (%)	2.65 (1.44–4.96)	2.30 (1.11–4.54)	2.38 (1.56–5.79)	0.666	2.36 (1.47–6.05)	2.37 (1.66–5.49)	5.06 (3.59–8.75)	0.068
Ovulation induction				0.220[a]				0.962[a]
Antagonist protocol	67 (79.8%)	16 (64.0%)	23 (88.5%)		66 (81.5%)	25 (92.6%)	23 (85.2%)	
Long protocol	10 (11.9%)	4 (16.0%)	2 (7.7%)		8 (9.9%)	2 (7.4%)	4 (14.8%)	
Short protocol	1 (1.2%)	0 (0.0%)	0 (0.0%)		1 (1.2%)	0 (0.0%)	0 (0.0%)	
Mild stimulation protocol	3 (3.6%)	2 (8.0%)	0 (0.0%)		2 (2.5%)	0 (0.0%)	0 (0.0%)	
Ultra-long protocol	3 (3.6%)	1 (4.0%)	0 (0.0%)		3 (3.7%)	0 (0.0%)	0 (0.0%)	
Natural cycle protocol	0 (0.0%)	2 (8.0%)	1 (3.8%)		1 (1.2%)	0 (0.0%)	0 (0.0%)	
No. of oocyte retrieved	12 (1–29)	11 (1–25)	8.5 (1–22)	0.058	16 (3–35)	14 (0–40)	12 (3–35)	0.067
Fertilization techniques				0.627				0.224
IVF	39 (46.4%)	14 (56.0%)	14 (53.8%)		53 (65.4%)	14 (51.9%)	20 (74.1%)	
ICSI	45 (53.6%)	11 (44.0%)	12 (46.2%)		28 (34.6%)	13 (48.1%)	7 (25.9%)	
Cycle types				0.206				0.930[a]
Fresh	18 (21.4%)	8 (27.6%)	3 (11.5%)		9 (11.1%)	4 (14.8%)	3 (11.9%)	
Frozen	66 (78.6%)	17 (68.0%)	23 (88.5%)		72 (88.9%)	23 (85.2%)	24 (88.9%)	
No. of embryos transferred				0.440				0.001*
1	53 (63.1%)	14 (56.0%)	19 (73.1%)		59 (72.8%)	9 (33.3%)	13 (48.1%)	
2	31 (36.9%)	11 (44.0%)	7 (26.9%)		22 (27.2%)	18 (66.7%)	14 (51.9%)	
Embryo type				0.900				< 0.001*
Cleavage embryo	33 (39.3%)	10 (40.0%)	9 (34.6%)		24 (29.6%)	21 (77.8%)	12 (44.4%)	
Blastocyst	51 (60.7%)	15 (60.0%)	17 (65.4%)		57 (70.4%)	6 (22.2%)	15 (55.6%)	

Table 1 (continued)

	Control ($n=135$)				PCOS ($n=135$)			
	Term delivery	Preterm delivery	Miscarriage	*P*-value	Term delivery	Preterm delivery	Miscarriage	*P*-value
Transferred embryo quality				0.033[a*]				0.492[a]
With high quality	81 (96.4%)	24 (96.0%)	21 (80.8%)		77 (95.1%)	24 (88.9%)	25 (92.6%)	
Without high quality	3 (3.6%)	1 (4.0%)	5 (19.2%)		4 (4.9%)	3 (11.1%)	2 (7.4%)	
Patients with pregnancy-related complications				0.002[*]				0.117[a]
Yes	30 (35.7%)	7 (28.0%)	0 (0%)		14 (17.3%)	6 (22.2%)	1 (3.7%)	
No	54 (64.3%)	18 (72.0%)	26 (100%)		67 (82.7%)	21 (77.8%)	26 (96.3%)	

Abbreviations PCOS, polycystic ovary syndrome; BMI, body mass index; FSH, follicle-stimulating hormone; LH, luteinizing hormone; Total T, total testosterone; Free T, free testosterone; SHBG, sex hormone-binding globulin; DHEAS, dehydroepiandrosterone sulfate; AMH, anti-müllerian hormone; FAI, free androgen index; IVF, in vitro fertilization; ICSI, intracytoplasmic sperm injection. Continuous Variables are shown as mean ± standard deviation or median (interquartile range). The analysis of variance was used for data with normal distribution and Kruskal-Wallis was used for testing independent samples. Categorical variables are presented as percentages (%) and analyzed by Chi-square test or Fisher's exact test. [a]Fisher's exact test, [*]*P*-value < 0.05

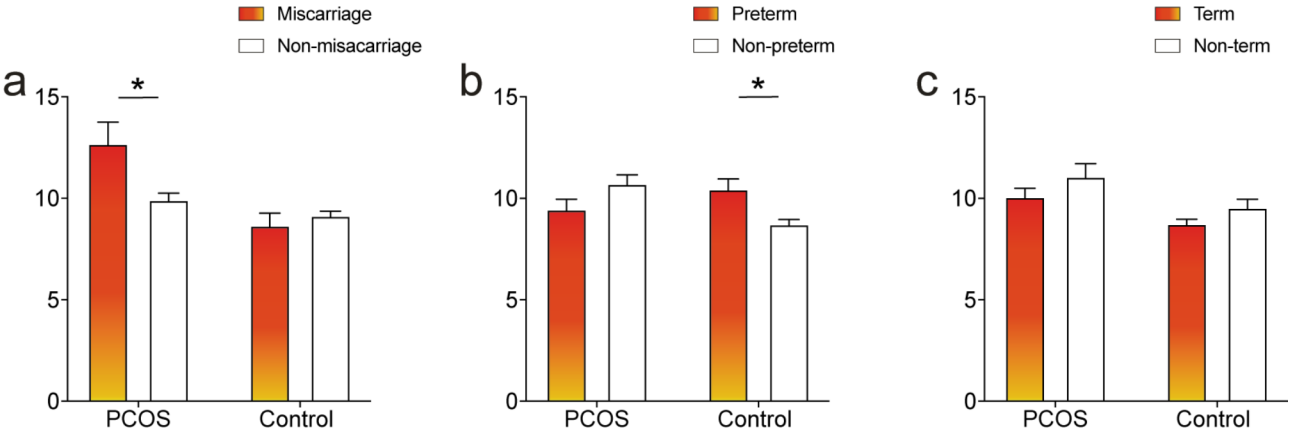

Fig. 1 Serum fructose levels in different pregnancy outcome groups. (**a**) Differences in serum fructose levels between miscarriage women and non-miscarriage patients with or without PCOS. (**b**) Differences in serum fructose levels between preterm birth women and non-preterm birth patients with or without PCOS. (**c**) Differences in serum fructose levels between term delivery women and non-term delivery patients with or without PCOS. PCOS, Polycystic ovary syndrome

discovered in the miscarriage group, whereas in women without PCOS, the preterm delivery group exhibited the highest serum fructose level. Moreover, we analyzed the differences in fructose concentrations between miscarriage and non-miscarriage groups, preterm delivery and non-preterm delivery groups, as well as term delivery and non-term delivery groups. Our findings revealed a notable difference in serum fructose levels between the miscarriage and the non-miscarriage groups in women with PCOS ($P=0.003$) (Fig. 1a). Simultaneously, a considerable difference in serum fructose levels between the preterm and non-preterm groups in the non-PCOS cohort ($P<0.001$) (Fig. 1b). However, within both the control and PCOS groups, there was no significant association observed between serum fructose levels and the rate of term delivery. ($P>0.05$) (Fig. 1c).

Subsequently, we conducted a more in-depth exploration of the association between fructose concentrations and three pregnancy outcomes. Among the basic hormones analyzed, a positive correlation was detected between fructose concentrations and serum DHEAS concentrations in patients with PCOS ($r=0.184$, $P=0.044$). In the control group, serum fructose levels were correlated with both serum DHEAS concentrations ($r=0.190$, $P=0.032$) and the free androgen index (FAI) (r = -0.260, $P=0.004$) as displayed in Supplementary Table 2. However, no significant variance in basic hormone levels were noted between different pregnancy outcomes within PCOS or non-PCOS group.

In summary, significant differences were identified in serum fructose levels among groups with varying pregnancy outcomes. Specifically, in patients with PCOS, those who experienced miscarriages had higher serum fructose levels compared to the non-miscarriage group. Similarly, among non-PCOS females, the preterm birth group exhibited elevated serum fructose levels relative to the term birth group. This correlation could not be attributed to changes in hormone levels.

Associations between serum Fructose levels and miscarriage rate in women with PCOS

Significant variations were observed in serum fructose levels among the three examined pregnancy outcomes, suggesting a potential link between fructose concentrations and reproductive consequences. To substantiate this link, a series of analytical procedures were undertaken.

The study population was stratified into four quartiles based on serum fructose levels within the cohort of patients with PCOS, to examine the influence of fructose on pregnancy outcomes. The quartiles were defined as follows: Quartile 1 (Q1) with fructose levels less than 8.26 μmol/L; Quartile 2 (Q2) ranging from 8.26 to 9.76 μmol/L; Quartile 3 (Q3) encompassing levels from 9.76 to 11.75 μmol/L; and Quartile 4 (Q4) consisting of levels equal to or greater than 11.75 μmol/L.

Notably, the analysis revealed a marked difference in miscarriage rates between these groups, with the incidence being significantly higher in the upper quintile ($P = 0.010$) as indicated in Table 2. However, no discernible differences in serum fructose levels were detected when comparing cases of early and late miscarriage. Subsequently, we conducted a Spearman analysis to explore the possible correlation between serum fructose levels and three pregnancy outcomes. The findings illuminated that fructose levels were positively linked to the miscarriage rate ($r = 0.258$, $P = 0.002$) among the PCOS population (Table 3). Lastly, logistic regression analysis was employed to further evaluate the findings. Univariate logistic regression analysis indicated that the incidence of miscarriage was significantly different between Q1 and Q4 in the PCOS group (odds ratio (OR) = 9.595, $P = 0.005$) (Table 4). Simultaneously, all relevant variables identified by univariate logistic regression, as well as personal baseline characteristics, including age and BMI, were incorporated in multivariate logistic regression analysis. A significant increase in miscarriage rates in Q4 compared to Q1 was indicated with an OR of 10.138 ($P = 0.005$), even after considering the age and BMI of patients. Finally, to assess the predictive value of serum fructose levels for miscarriage in women with PCOS, ROC curves were applied. The AUC of fructose for miscarriage diagnosis in women with PCOS was 0.686 (Fig. 2; Table 5), and this indicator could diagnose miscarriage with a sensitivity of 66.7% and a specificity of 70.4%.

Taken together, the miscarriage rate is higher in individuals with elevated serum fructose levels compared to those with lower fructose levels in PCOS group.

Associations between serum Fructose levels and preterm delivery rate in women without PCOS

As previously stated, the identical analytical methodology was also applied to the non-PCOS cohort. Participants in the non-PCOS group were categorized into four groups based on the quartile of serum fructose levels: Q1 ≤ 7.42 μmol/l; Q2: 7.42–8.56 μmol/l; Q3: 8.56–10.09 μmol/l; Q4: ≥ 10.09 μmol/l.

A significant variation in the frequency of preterm deliveries was observed among different fructose level categories in women without PCOS ($P < 0.001$) (Table 2). However, among the different types of preterm birth, serum fructose levels did not show any significant differences. Furthermore, serum fructose levels were correlated with neonatal birthweight ($P = 0.008$) and the incidence of pregnancy complications ($P = 0.007$), including gestational diabetes and pregnancy-induced hypertension. The Spearman analysis revealed a correlation of serum fructose levels with preterm birth ($r = 0.311$, $P < 0.001$) and birthweight (r = -0.266, $P = 0.005$) in the non-PCOS population (Table 3). Furthermore, our analysis demonstrates a significant variance in the preterm birth rates between Q1 and Q4, with univariate logistic regression indicating an OR of 23.100 ($P = 0.003$). This finding is substantiated by multivariate logistic regression analysis (OR = 18.359, $P = 0.008$) (Table 4) after adjusting for several co-variables, including ovulation induction protocol, age, and BMI. Ultimately, ROC curves were employed to evaluate the prognostic efficacy of serum fructose levels regarding preterm birth among non-PCOS individuals. The AUC for diagnosing preterm birth via fructose in this cohort reached 0.731 (Fig. 2; Table 5), with the capacity to identify miscarriage at a sensitivity of 56.0% and specificity of 83.6%.

In summary, individuals with elevated serum fructose levels have a higher rate of preterm delivery compared to women with low serum fructose levels among patients without PCOS.

Discussion

This study represents the first investigation of the association between serum fructose concentrations and pregnancy outcomes in patients with or without PCOS. The primary findings can be summarized as follows: Serum fructose levels exhibit a positive correlation with miscarriage in patients with PCOS, while in women without PCOS, a positive correlation is observed between serum fructose levels and preterm birth.

Existing literature supports these findings. The increase in fructose intake is increasingly recognized as a contributing factor to the global obesity epidemic [20]. Additionally, obese pregnant women are more prone to experiencing early miscarriages and an elevated risk of congenital fetal anomalies [21], such as neural tube

Table 2 Pregnancy outcomes and complications among different serum Fructose status

	Fasting serum fructose levels				
	Quartile 1	**Quartile 2**	**Quartile 3**	**Quartile 4**	***P*-value**
PCOS					
Fructose (pmol/μL)	< 8.26	8.26–9.76	9.76–11.75	≥ 11.75	
N	33	34	34	34	
Total miscarriage	2 (6.1)	6 (17.6)	6 (17.6)	13 (38.2)	0.010*
Miscarriage					0.557[a]
Early miscarriage	1 (50.0)	4 (66.7)	4 (66.7)	11 (84.6)	
Late miscarriage	1 (50.0)	2 (33.3)	2 (33.3)	2 (15.4)	
Term delivery	24 (72.7)	20 (58.8)	20 (58.8)	17 (50.0)	0.298
Preterm delivery	7 (21.2)	8 (23.5)	8 (23.5)	4 (11.8)	0.572
Preterm delivery					0.313[a]
≥ 34 and < 37 weeks	6 (85.7)	8 (100.0)	5 (62.5)	3 (75.0)	
≥ 32 and < 34 weeks	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
< 32 weeks	1 (14.3)	0 (0.0)	3 (37.5)	1 (25.0)	
Delivery type					0.331[a]
Cesarean	24 (77.4)	24 (85.7)	21 (77.8)	19 (95.0)	
Eutocia	7 (22.6)	4 (14.3)	6 (22.2)	1 (5.0)	
Pregnancy complications	3 (9.1)	10 (29.4)	4 (11.8)	4 (11.8)	0.080
Gestational diabetes mellitus	2 (6.1)	5 (14.7)	2 (5.9)	2(5.9)	0.547[a]
Pregnancy-induced hypertension	1 (3.0)	5 (14.7)	2 (5.9)	4 (11.8)	0.367[a]
Birthweight (g)	3500 (3100–3800)	3474 (3025–3975)	3300 (2750–3650)	3270 (3200–3550)	0.396
Control					
Fructose (pmol/μL)	≤ 7.42	7.42–8.56	8.56–10.09	≥ 10.09	
N	34	33	34	34	
Total miscarriage	10 (29.4)	5 (15.2)	6 (17.6)	5 (14.7)	0.373
Miscarriage					0.711[a]
Early miscarriage	7 (70.0)	5 (100.0)	5 (83.3)	3 (75.0)	
Late miscarriage	3 (30.0)	0 (0.0)	1 (16.7)	1 (25.0)	
Term delivery	23 (67.6)	22 (66.7)	24 (70.6)	15 (44.1)	0.091
Preterm delivery	1 (2.9)	6 (18.6)	4 (11.8)	14 (41.2)	< 0.001*
Preterm delivery					0.469[a]
≥ 34 and < 37 weeks	1 (100.0)	5 (100.0)[a]	2 (50.0)	9 (63.3)	
≥ 32 and < 34 weeks	0 (0.0)	0 (0.0)	2 (50.0)	2 (14.3)	
< 32 weeks	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)	
Delivery type					0.167[a]
Cesarean	22 (91.7)	24 (88.9)	20 (71.4)	26 (89.7)	
Eutocia	2 (8.3)	3 (11.1)	8 (28.6)	3 (10.3)	
Pregnancy complications	6 (17.6)	8 (24.2)	17 (50.0)	6 (17.6)	0.007*
Gestational diabetes mellitus	5 (14.7)	3(9.1)	9 (26.5)	3 (8.8)	0.160[a]
Pregnancy-induced hypertension	2 (5.9)	5 (15.2)	8 (23.5)	4 (11.8)	0.212[a]
Birthweight (g)	3443 ± 453	3339 ± 569	3346 ± 644	2906 ± 740	0.008*

Abbreviations PCOS, polycystic ovary syndrome. Normally distributed continuous variables were reported as mean ± standard deviation and analyzed by analysis of variance, as well as non-normally distributed continuous variables were reported as the median (interquartile range) and analyzed by Kruskal-Wallis test. Categorical variables are presented as percentages (%) and analyzed by Chi-square test or Fisher's exact test. [a]Fisher's exact test, *P-value < 0.05

defects, which in turn heighten the likelihood of preterm birth [22]. Furthermore, the rise in fructose intake is linked to gestational diabetes [16], a condition that has been linked to an increased risk of preterm birth [23]. In the pathological context of preeclampsia, hypoxic placenta drives endogenous fructose production through the activation of aldose reductase and HIF1α expression. This excessive fructose accumulation, along with its positive feedback in driving certain clinical features of preeclampsia [24], contributes to the increased risk of adverse pregnancy outcomes [25].

Moreover, increased maternal fructose consumption can impair endometrial decidualization, leading to an unfavorable uterine environment that is inadequate for supporting proper embryonic development and ultimately resulting in miscarriage [17]. Maternal

Table 3 Correlation of serum Fructose levels with pregnancy outcomes and complications

	PCOS		Control	
	r	*P*-value	*r*	*P*-value
Maternal age (y)	-0.003	0.974	0.118	0.174
Maternal BMI (kg/m^2)	-0.078	0.370	-0.044	0.610
Miscarriage	0.258	0.002*	-0.117	0.177
Preterm delivery	-0.079	0.362	0.311	< 0.001*
Term delivery	-0.146	0.090	-0.154	0.074
Delivery type	-0.137	0.161	0.045	0.643
Pregnancy complications	0.090	0.365	0.076	0.437
Gestational diabetes mellitus	-0.099	0.255	-0.020	0.820
Pregnancy-induced hypertension	-0.013	0.884	0.085	0.329
Birthweight (g)	-0.112	0.260	-0.266	0.005*

Abbreviations BMI, body mass index. *P*-value were tested with Spearman analysis. *P-value < 0.05

high-fructose diets lead to fetal growth restriction and inefficient placental function, culminating in adverse pregnancy outcomes [26]. To our knowledge, there is currently no established intervention specifically targeting uterine factors in PCOS [27]. Therefore, modulating fructose levels represents a potential therapeutic strategy for preventing miscarriage in pregnant women with PCOS.

Lastly, studies have reported that fructose can reprogram cellular metabolic pathways to promote glutamine breakdown and oxidative metabolism, which are essential for the increased production of inflammatory cytokines in human monocytes treated with lipopolysaccharide and mouse macrophages [24]. This highlights the pro-inflammatory effects of fructose, which can ultimately lead to adverse pregnancy outcomes [25].

Compared to the PCOS group, a higher incidence of pregnancy-related complications was observed in the control group. This difference may be partly attributable to the older mean age of the control group (32 years) compared to the PCOS group (30 years). Additionally, the more intensive preconception and prenatal management received by women with PCOS likely contributed to the reduced occurrence of complications. Moreover, in the logistic regression analysis, it was found that, in addition to age and BMI, the ovulation induction protocol was a potential confounding factor. The selection of ovulation induction regimens is primarily focused between the

Table 4 Logistic analysis of serum Fructose levels and risk of pregnancy outcomes

Outcomes	Fructose (pmol/μL)	Univariate regression			Multivariate regression		
		OR	95% CI	*P*-value	Adjusted OR	95% CI	*P*-value
PCOS							
Miscarriage	< 8.26	1.000	-	-	1.000	-	-
	8.26–9.76	3.321	0.619–17.820	0.161	3.689	0.671–20.278	0.133
	9.76–11.75	3.321	0.619–17.820	0.161	2.410	0.632–18.412	0.154
	≥ 11.75	9.595	1.960-46.978	0.005*	10.138	2.036–50.470	0.005*
Preterm delivery	< 8.26	1.000	-	-	1.000	-	-
	8.26–9.76	1.143	0.362–3.612	0.820	1.799	0.483–6.704	0.382
	9.76–11.75	1.143	0.362–3.612	0.820	1.040	0.283–3.815	0.953
	≥ 11.75	0.495	0.130–1.884	0.303	0.630	0.148–2.686	0.532
Term delivery	< 8.26	1.000	-	-	1.000	-	-
	8.26–9.76	0.536	0.192–1.495	0.233	0.359	0.112–1.147	0.084
	9.76–11.75	0.536	0.192–1.495	0.233	0.809	0.254–2.574	0.720
	≥ 11.75	0.375	0.1351.039	0.059	0.216	0.068–0.683	0.009*
Control							
Miscarriage	≤ 7.42	1.000	-	-	1.000	-	-
	7.42–8.56	0.429	0.129–1.429	0.168	0.312	0.076–1.280	0.106
	8.56–10.09	0.514	0.163–1.624	0.257	0.404	0.091–1.788	0.233
	≥ 10.09	0.414	0.124–1.377	0.150	0.325	0.080–1.323	0.117
Preterm delivery	≤ 7.42	1.000	-	-	1.000	-	-
	7.42–8.56	7.333	0.831–64.694	0.073	6.722	0.753–60.071	0.088
	8.56–10.09	4.400	0.465–41.596	0.196	4.220	0.439–40.568	0.212
	≥ 10.09	23.100	2.819-189.283	0.003*	18.359	2.162-155.864	0.008*
Term delivery	≤ 7.42	1.000	-	-	1.000	-	-
	7.42–8.56	0.957	0.345–2.652	0.932	1.025	0.364–2.889	0.962
	8.56–10.09	1.148	0.410–3.214	0.793	1.232	0.429–3.538	0.698
	≥ 10.09	0.378	0.141–1.013	0.053	0.422	0.155–1.152	0.092

Abbreviations PCOS, polycystic ovary syndrome; OR, odds ratio; CI, confidence interval. *P-value < 0.05

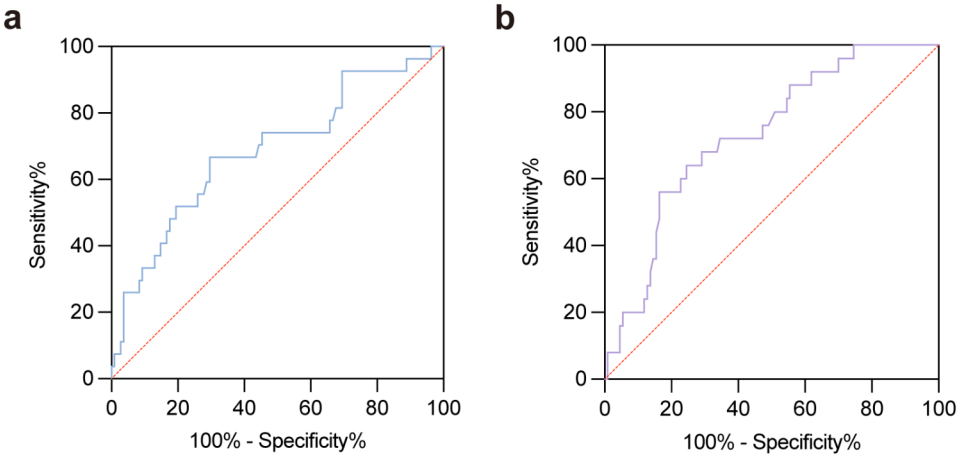

Fig. 2 Diagnostic performance of serum fructose levels in patients with or without PCOS. (**a**) ROC curves illustrate the value of serum fructose levels in predicting miscarriage among women with PCOS. (**b**) ROC curves illustrate the value of serum fructose levels in predicting preterm birth among women without PCOS. PCOS, Polycystic ovary syndrome; ROC, Receiver operating characteristic

Table 5 Prediction value of serum Fructose levels in the pregnancy outcome of patients with or without PCOS

Population	Pregnancy outcome	AUC	95% CI	Sensitivity%	Specificity%	Cutoff value	PPV%	NPV%
PCOS	Miscarriage	0.686	0.568–0.805	66.7	70.4	10.49	69.3	67.9
Control	Preterm birth	0.731	0.630–0.832	56.0	83.6	10.19	77.3	65.5

Abbreviations PCOS, polycystic ovary syndrome; AUC, the area under the curve; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value

antagonist protocol and the long protocol; however, more definitive conclusions necessitate larger-scale studies.

In this study, we differentiated between women with and without PCOS to comprehensively demonstrate the potential influence of elevated serum fructose levels on pregnancy outcomes. One contributing factor may be that PCOS, as an endocrinopathy and metabolic disorder, is associated with increased rates of miscarriage and preterm birth [7, 8]. Additionally, our data revealed that, beyond the differences in fructose levels, there are disparities in various hormones such as FSH, LH, and DHEAS between the PCOS and control groups. These hormonal variations may contribute to the observed correlation between fructose levels and divergent pregnancy outcomes in the PCOS group compared to the non-PCOS group (Supplementary Table 1).

Individuals with PCOS often exhibit metabolic abnormalities, such as insulin resistance and hyperandrogenemia [2]. These metabolic disturbances may lead to a decline in oocyte quality [4] and endometrial receptivity [5], thereby increasing the risk of miscarriage. Chronic inflammation and oxidative stress are commonly present in patients with PCOS [2], which may affect embryo implantation and the stability of early pregnancy. Metabolites produced during fructose metabolism, such as uric acid [28], may further exacerbate inflammatory responses, thus increasing the risk of miscarriage. Moreover, the more intensive preconception and prenatal management in women with PCOS likely contributes to the lower occurrence of complications and consequently lowers the risk of preterm birth. In the control group, relying on better oocyte quality and uterine function, the impact of increased fructose concentration seems insufficient to increase the risk of miscarriage. However, its effects on pregnancy complications, such as gestational diabetes and preeclampsia [24], may contribute to the risk of preterm birth. Nevertheless, precise mechanisms require further investigation.

The primary strength of this article lies in its pioneering exploration of the association between serum fructose levels and pregnancy outcomes in patients with or without PCOS. Additionally, we gather comprehensive patient-related information and analyze biological markers. These markers are adjusted in logistic regression to reduce bias and enhance the reliability of outcomes. Despite these strengths, several limitations exist in our study. Firstly, it was conducted at a single center, necessitating further verification through future multicenter studies. Secondly, our study exclusively focused on patients undergoing assisted reproductive techniques, and the sample size was modest. As a result, our results can only be applied to a certain demographic. Lastly, serum fructose levels were measured prior to pregnancy, potentially introducing experimental bias due to fluctuations in these levels during pregnancy.

Conclusions

In summary, our study elucidates the correlation between serum fructose levels and adverse pregnancy outcomes in IVF patients. Specifically, in patients with PCOS, elevated

serum fructose levels are linked to miscarriage, while in the non-PCOS cohort, these levels are related to a higher incidence of preterm birth. The potential use of serum fructose levels as a predictive biomarker holds promise for early detection and clinical intervention, aiming to improving maternal and fetal health. Furthermore, existing evidence suggests that elevated fructose levels may contribute to adverse pregnancy outcomes through various mechanisms. Additional research is warranted to establish a comprehensive understanding of the role of fructose and its implications for adverse pregnancy outcomes.

Abbreviations

PCOS	Polycystic ovary syndrome
GnRH	Gonadotropin-releasing hormone
BMI	Body mass index
Total T	Total testosterone
LH	Luteinizing hormone
FSH	Follicle-stimulating hormone
AMH	Anti-Müllerian hormone
DHEAS	Dehydroepiandrosterone sulfate
SHBG	Sex hormone-binding globulin
CVs	Coefficients of variation
OR	Odds ratio

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions

Conceptualization, D.L., Z.N. AND Y.F.; methodology, D.L AND Z.N.; formal analysis, Z.N. AND B.Z.; investigation, Y.F. AND J.S.; writing—original draft preparation, B.Z. Y.L. Y.L.; writing—review and editing, D.L. AND Z.N.; visualization, J.S. AND Y.F.; project administration, D.L. and Z.N.; funding acquisition, D.L. and Z.N. All authors have read and agreed to the published version of the manuscript.

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Data availability

The analyzed data sets generated during the present study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the principles of the Declaration of Helsinki. The present study was approved by the Institutional Review Board of China Medical University (approval number 2020PS198K). All participants were exempted from providing informed consent, as the patient specimens used in the study were all discarded specimens after routine clinical diagnosis, and privacy-related information was removed.

Consent for publication

All authors are consent for publication.

Competing interests

The authors declare no competing interests.

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