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Uric Acid and Metabolic Phenotype in Placental Complications After Programmed Frozen Embryo Transfer

Sevara Sh. Rakhmanova^{1,2,*}, Makhira L. Saipova², Feruza D. Karimova²

¹ Central Asian University, Tashkent, Uzbekistan.

² Center for the Development of Professional Qualifications of Medical Workers, Ministry of Health of the Republic of Uzbekistan, Tashkent, Uzbekistan.

Sevara Sh. Rakhmanova (affiliations 1, 2): ORCID 0009-0001-5003-4386.

Makhira L. Saipova (affiliation 2): ORCID 0009-0006-5105-8669.

Feruza D. Karimova (affiliation 2): ORCID 0009-0007-3645-2972.

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* Corresponding author: Dr. Sevara Sh. Rakhmanova, PhD

Center for the Development of Professional Qualifications of Medical Workers, Parkent Street 51, 100007 Tashkent, Uzbekistan., E-mail: sevara.rakhmanova91@mail.ru.

ABSTRACT: Programmed frozen embryo transfer (FET) is associated with increased obstetric risk, but the contribution of maternal metabolic characteristics remains uncertain. We examined first-trimester serum uric acid, metabolic phenotype and subsequent placental complications in a retrospective cohort of 158 singleton pregnancies after programmed FET with autologous oocytes, delivered in Tashkent, Uzbekistan, during 2022–2024. Metabolic phenotype was defined as pre-pregnancy body mass index ≥ 30 kg/m² and/or homeostasis model assessment of insulin resistance (HOMA-IR) ≥ 2.5 . The primary composite comprised pre-eclampsia, recorded placental dysfunction with abnormal uteroplacental Doppler, or placental abruption. Uric acid was measured at 8+0–12+6 weeks. The metabolic phenotype was present in 82 pregnancies, and 54 pregnancies (34.2%) developed the composite outcome. Median uric acid was higher with versus without the phenotype (211.5 versus 176.5 $\mu\text{mol/L}$) and with versus without the composite outcome (222.5 versus 180.0 $\mu\text{mol/L}$; both $p < 0.001$). The adjusted odds ratio per 10 $\mu\text{mol/L}$ was 1.45 (95% confidence interval 1.24–1.69). The phenotype estimate attenuated from 3.69 unadjusted to 1.29 (0.52–3.22) after adjustment. Apparent discrimination was 0.809 for uric acid alone and 0.824 for the multivariable model, with an optimism-corrected model area of 0.802. Among 156 women without pregestational diabetes, metabolic phenotype remained associated with recorded gestational diabetes. Early uric acid was associated with subsequent placental complications within this cohort; these findings do not establish mediation, clinical screening utility or benefit from urate lowering.

1 INTRODUCTION

Endometrial preparation for frozen embryo transfer (FET) may use an ovulatory cycle or exogenous oestradiol and progesterone in a programmed cycle. Cohort studies have associated programmed FET with greater risks of hypertensive disorders and other obstetric complications than ovulatory FET (Ginström Ernstad et al., 2019; Saito et al., 2019). Systematic

reviews support this association, although treatment selection, heterogeneous protocols and maternal characteristics complicate causal interpretation (Busnelli et al., 2022; Zaat et al., 2023). Understanding variation in risk within programmed FET pregnancies may therefore complement comparisons between cycle types.

The absence of a corpus luteum provides one possible explanation. In addition to progesterone, the corpus luteum produces vasoactive factors, including relaxin, that may contribute to maternal cardiovascular adaptation. Reduced aortic compliance and increased pre-eclampsia risk have been observed in pregnancies conceived without a corpus luteum (von Versen-Höynck et al., 2019). These observations support investigation of endocrine and vascular mechanisms, but do not establish that corpus luteum absence explains all excess risk (Conrad et al., 2022). Obesity, insulin resistance and other maternal characteristics may also influence both treatment selection and pregnancy outcomes.

Uric acid is an endogenous product of purine metabolism with context-dependent antioxidant and pro-oxidant actions. Experimental studies link increased urate to impaired nitric oxide availability and elevated blood pressure (Khosla et al., 2005; Mazzali et al., 2001). Reviews describe possible interactions with endothelial dysfunction and placental pathology (Kanellis and Kang, 2005; Bainbridge and Roberts, 2008). Serum concentration also depends on renal handling: insulin resistance has been associated with reduced urinary uric acid clearance (Facchini et al., 1991). A serum measurement may consequently reflect several physiological processes rather than a single causal pathway.

Early-pregnancy uric acid has been associated with later pre-eclampsia and gestational diabetes in observational studies (Laughon et al., 2009, 2011; Colmenares-Mejia et al., 2023; Yue et al., 2023). Whether uric acid contributes information beyond maternal metabolic phenotype within programmed FET pregnancies remains uncertain. Because every pregnancy in the present cohort followed programmed FET, this study examines variation within that protocol; it cannot estimate an effect of programmed versus natural-cycle FET or of corpus luteum absence itself.

We asked whether first-trimester uric acid was associated with maternal metabolic phenotype and subsequent placental complications after programmed FET, whether the association persisted after accounting for age and transfer characteristics, and whether similar associations were observed for gestational diabetes. Embryo stage and embryo number were examined as exploratory treatment characteristics.

2 MATERIALS AND METHODS

2.1 Study design and participants

This retrospective cohort comprised 158 singleton pregnancies conceived by programmed FET with autologous oocytes at Two-line Fertility, Tashkent, Uzbekistan, with antenatal care and delivery at the Republican Perinatal Center. Deliveries occurred between 1 January 2022 and 31 December 2024. Eligibility required a programmed frozen transfer, singleton pregnancy and an available first-trimester biochemical panel. Donor-oocyte pregnancies, multiple gestations and natural or modified natural-cycle transfers were not eligible. The analysis included all 158 records in the available study dataset; the number screened before selection and exclusions by reason were not available for reconstruction. Accordingly, selection completeness and the representativeness of the cohort could not be established.

Endometrial preparation was recorded as oral oestradiol, 2–6 mg/day for 10–14 days, followed by vaginal micronised progesterone, 100–600 mg/day. The preparation followed a programmed, non-ovulatory protocol. Direct ultrasound documentation of corpus luteum absence was not available in the analysis dataset, so this characteristic was inferred from the recorded protocol. Transfers involved cleavage-stage embryos on day 3 or blastocysts on day 5, and one or two embryos were transferred. The cohort was restricted to singleton pregnancies at delivery; early vanishing-twin status was not available. Reporting was informed by the STROBE recommendations (von Elm et al., 2007).

2.2 Laboratory measurements and metabolic phenotype

Serum uric acid and creatinine were recorded at the first antenatal visit. The documented uric acid method was an automated uricase–peroxidase enzymatic colorimetric assay. The analyser model, reagent manufacturer, analytical imprecision and laboratory quality-control data were unavailable. The dataset notes specified a local reference interval of 150–350 $\mu\text{mol/L}$; its trimester-specific validation could not be established. Uric acid was therefore analysed continuously and by cohort-based categories, rather than classified using this interval as a validated pregnancy threshold.

Pre-pregnancy body mass index (BMI) was calculated as weight in kilograms divided by squared height in metres. HOMA-IR was calculated from recorded fasting insulin and glucose as $\text{insulin } (\mu\text{IU/mL}) \times \text{glucose (mmol/L)} / 22.5$ (Matthews et al., 1985). BMI and HOMA-IR values were consistent with the workbook calculations, rounded to one and two decimal places, respectively. The metabolic phenotype was defined for this analysis as $\text{BMI} \geq 30 \text{ kg/m}^2$ and/or $\text{HOMA-IR} \geq 2.5$. This HOMA-IR threshold was an operational research definition and was not locally validated as a clinical diagnosis in pregnancy. The phenotype should not be interpreted as a comprehensive diagnosis of metabolic syndrome.

Phenotype groups were derived from the calculated variables rather than participant-code prefixes or the original group column. Two participants changed group relative to the stored label, leaving 82 with and 76 without the phenotype. Original group labels were retained for sensitivity analysis. No patient-level values were imputed or replaced in this reanalysis.

Sampling gestational age was stored as weeks.days, where 10.4 denotes 10 weeks and 4 days. It was converted to decimal weeks as completed weeks plus additional days divided by seven before numerical analysis. Gestational age at delivery was already stored as decimal weeks. Sampling dates, delivery dates and gestational ages reconciled to within one day. The recorded sampling window was 8+0–12+6 weeks.

2.3 Outcomes and prophylaxis

The primary endpoint for this analysis was a composite of recorded pre-eclampsia, placental dysfunction accompanied by abnormal uteroplacental Doppler, or placental abruption. Participants with more than one component were counted once. Placental dysfunction without an abnormal Doppler flag did not fulfil that component. Pre-eclampsia was recorded as a clinical diagnosis, described in the study documentation with reference to the ISSHP recommendations (Magee et al., 2022). Blood pressure, proteinuria, disease onset and organ-dysfunction measurements were not included in the analysis dataset, preventing independent re-adjudication of these diagnoses.

Uterine and umbilical artery pulsatility indices were recorded during routine ultrasound examinations by one sonographer. The study documentation described abnormal uteroplacental flow as a uterine artery pulsatility index above the gestational-age-specific 95th centile in the clinical report. However, examination dates, gestational ages, the exact reference chart and source images were unavailable for this analysis. We therefore used the recorded abnormal-flow classification without reclassifying participants from an absolute index cut-off. Numerical indices were assessed only descriptively. This component is a clinical-record endpoint and not an independently validated measure of placental insufficiency.

Secondary outcomes comprised the individual components, any recorded hypertensive disorder, gestational hypertension, gestational diabetes, preterm delivery, caesarean delivery and recorded neonatal outcomes. Preterm delivery was defined as <37 completed weeks, macrosomia as birth weight $\geq 4000 \text{ g}$, and low birth weight as $<2500 \text{ g}$. Low birth weight was not equated with small for gestational age. Intrauterine hypoxia, intrapartum fetal distress and early neonatal complications were analysed as recorded diagnoses. The workbook did not contain the complete oral glucose tolerance test results or the timing and diagnostic criteria for gestational diabetes. Gestational diabetes analyses excluded both women with recorded pregestational diabetes, including one also labelled as having gestational diabetes, leaving 156 eligible women and 36 recorded cases.

All women had a low-dose aspirin prescription recorded, with initiation at 12–14 completed weeks. This reflects prescribed treatment rather than verified intake; dose, adherence and duration were unavailable. Sampling preceded the recorded initiation week in 152 women. In six, sampling and initiation occurred within the same completed week, so their order could not be established. These six were excluded in a sensitivity analysis. The dataset notes described clinical eligibility with reference to USPSTF risk factors (US Preventive Services Task Force, 2021), but the additional history fields were selectively abstracted for 18 women and were not used to estimate cohort-wide risk-factor prevalence.

2.4 Statistical analysis

Continuous variables were summarised by median and interquartile range (IQR), and compared using two-sided Mann–Whitney U tests. These tests assess distributional differences and were not interpreted as tests solely of medians. Selected uric acid contrasts were quantified by the Hodges–Lehmann location-shift estimate, the median of all between-group pairwise differences, with percentile bootstrap 95% confidence intervals (CIs) from 2000 within-group resamples. This estimate need

not equal the difference between the two sample medians. Cliff's delta described the direction and magnitude of the distributional contrast. Associations between continuous variables were assessed using Spearman correlation.

Categorical variables were reported as n/N (%). Pearson's chi-square test without continuity correction was used when every expected cell count was at least five; otherwise, Fisher's exact test was used. Unadjusted risk ratios (RRs) used log-scale Katz intervals. The primary composite comparison was reported separately. Benjamini–Hochberg adjusted p values were calculated across all 16 secondary binary outcome comparisons, including caesarean delivery (Benjamini and Hochberg, 1995). Other comparisons, correlations, secondary regressions, interactions and sensitivity analyses were exploratory, with unadjusted p values. Variables defining the phenotype, and their direct components, were described without inferential p values. The study was not treated as a prospectively registered confirmatory analysis.

Binary logistic regression estimated odds ratios (ORs) with Wald 95% CIs. Uric acid was scaled per 10 $\mu\text{mol/L}$. Models included uric acid alone; uric acid with metabolic phenotype; and a five-predictor model adding maternal age, embryo stage and embryo number. These variables addressed metabolic and transfer-related associations, without automated significance-based selection. A further exploratory model replaced phenotype with continuous BMI and HOMA-IR and included age. ORs describe odds and were not interpreted as risk ratios. Attenuation of the phenotype coefficient was not interpreted as evidence of mediation.

The five-predictor model had 54 events, or 10.8 events per slope parameter, a descriptive ratio that does not guarantee freedom from overfitting. Model checks included variance inflation factors, a quadratic uric acid term and separate uric acid interactions with phenotype, stage and embryo number, each assessed by a likelihood-ratio test against the corresponding model without that term. The Hosmer–Lemeshow test used ten approximately equal groups of fitted probabilities; absence of a significant result was not considered proof of calibration. Uric acid categories were based on sample tertile boundaries, with ties kept together. Trend used the Cochran–Armitage test with scores 1, 2 and 3.

Receiver operating characteristic (ROC) areas and comparisons were calculated using DeLong covariance estimates (DeLong et al., 1988). CIs for the fitted multivariable score describe apparent performance and do not account for model-development uncertainty. Internal validation refitted the five-predictor model in 1000 ordinary bootstrap samples; optimism was the bootstrap-sample area minus the area obtained by applying that fitted model to the original sample. The mean was subtracted from the original apparent area. Of 1000 fits, 993 yielded estimable covariance matrices; seven non-estimable fits were excluded. The data-derived uric acid threshold maximised Youden's index, using the lowest threshold in a tie. Its bootstrap percentile interval used 1000 samples. Sensitivity, specificity and predictive-value CIs were exact Clopper–Pearson intervals conditional on the selected threshold, and do not account for threshold selection.

Sensitivity models included uric acid and phenotype, with one additional covariate at a time: creatinine, daily oestradiol dose, polycystic ovary syndrome (PCOS), or sampling gestational age. We also examined original group labels; exclusion of chronic hypertension, pregestational diabetes or previous pre-eclampsia; exclusion of ambiguous aspirin timing; and restriction to single-embryo or blastocyst transfers. Separate models assessed the uric acid/creatinine ratio per 0.1 unit and phenotype-specific uric acid slopes. These were limited adjustment analyses, not simultaneous control for all potential confounders.

Analyses were performed in Python 3 using NumPy, SciPy and statsmodels. Logistic regression used maximum-likelihood estimation with iteratively reweighted least squares. Bootstrap analyses used reproducible random seeds. The reported analysis variables were complete for all included records, with the GDM eligibility restriction described above. Selectively unabstracted history fields were not treated as negative findings. Statistical significance was assessed at 0.05, with attention to effect sizes, uncertainty and multiplicity.

2.5 Ethics

The study was approved by the Institutional Ethics Committee of the Republican Perinatal Center (IEC/RPC/2022/01, protocol No. 01/2022, decision dated 12 January 2022) and was conducted in accordance with the Declaration of Helsinki (2013 revision). Individual informed consent was waived for this retrospective analysis of de-identified records. The research dataset uses study codes and excludes names, medical-record numbers and dates of birth.

3 RESULTS AND DISCUSSION

3.1 Cohort characteristics and metabolic phenotype

The cohort included 52 deliveries in 2022, 49 in 2023 and 57 in 2024. Median maternal age was 34.0 years, and 86 women (54.4%) were nulliparous. The metabolic phenotype was present in 82 women (51.9%): 60 had BMI ≥ 30 kg/m², 52 had HOMA-IR ≥ 2.5 , and 30 met both criteria. Table 1 summarises the baseline characteristics. The comparison groups had similar observed age distributions, but this does not establish equivalence or balance of all confounders. PCOS was more frequent in the phenotype group, occurring in 23/82 versus 6/76 women (28.0% versus 7.9%).

Daily oestradiol dose and first-trimester creatinine were also higher in the phenotype group. Median creatinine was 68 versus 56 $\mu\text{mol/L}$ and median oestradiol dose was 6 versus 4 mg/day. The reasons for dose selection were not established by the dataset, and the dose difference cannot be attributed specifically to impaired endometrial response. Blastocyst transfers accounted for 73/82 and 66/76 pregnancies, respectively, while two embryos were transferred in 11/82 and 12/76. Similar observed transfer proportions do not eliminate confounding by treatment selection.

3.2 Distribution of first-trimester uric acid

Median sampling gestational age was 10.1 decimal weeks (IQR 9.3–11.0). Median uric acid was 193.5 $\mu\text{mol/L}$ (IQR 170.2–219.5; range 121–310). No value exceeded the upper limit stated in the local notes, but ten were below its lower limit. The local reference interval was not used as a validated clinical risk threshold.

Uric acid was higher with versus without the metabolic phenotype: medians 211.5 and 176.5 $\mu\text{mol/L}$, respectively, with a Hodges–Lehmann location shift of 35.0 $\mu\text{mol/L}$ and Cliff's delta of 0.59. It was also higher in pregnancies with the subsequent composite outcome: 222.5 versus 180.0 $\mu\text{mol/L}$, with a location shift of 38.0 $\mu\text{mol/L}$ and delta of 0.62 (both $p < 0.001$; Table 2 and **Figure 1**). No statistically detectable difference was found by embryo stage ($p = 0.422$) or embryo number ($p = 0.846$); the smaller strata limit precision.

Uric acid correlated with BMI (Spearman $\rho = 0.566$), HOMA-IR ($\rho = 0.283$), fasting insulin ($\rho = 0.274$) and creatinine ($\rho = 0.390$). Its association with fasting glucose was weak ($\rho = 0.039$, $p = 0.629$). The correlation with uterine artery pulsatility index was 0.391, but the absence of Doppler gestational ages limits interpretation. Uric acid was inversely associated with sampling gestational age ($\rho = -0.179$, $p = 0.024$), supporting the inclusion of sampling timing in sensitivity analysis without establishing a within-person trajectory.

3.3 Placental and other pregnancy outcomes

The composite outcome occurred in 54/158 pregnancies (34.2%; Wilson 95% CI 27.2–41.9%). Component counts were 26 pre-eclampsia, 36 placental dysfunction with abnormal Doppler and six abruption, with overlap. The recorded placental-dysfunction diagnosis alone was present in 43 women, seven of whom did not meet its Doppler requirement. Composite incidence was 39/82 (47.6%) with the phenotype and 15/76 (19.7%) without it (RR 2.41, 95% CI 1.45–4.00; $p < 0.001$; Table 3).

After excluding pregestational diabetes, recorded gestational diabetes occurred in 28/80 women with the phenotype and 8/76 without it (35.0% versus 10.5%; RR 3.33, 95% CI 1.62–6.83). Across the 16 secondary binary comparisons, gestational diabetes, placental dysfunction and abnormal uteroplacental Doppler retained adjusted p values below 0.05. Pre-eclampsia, macrosomia and intrauterine hypoxia each had an adjusted p value of approximately 0.052. These phenotype comparisons did not meet the 5% false-discovery threshold. The remaining secondary comparisons were also above that threshold. Continuous outcomes are reported separately as exploratory observations.

3.4 Uric acid gradient and adjusted associations

Composite incidence increased across the uric acid categories from 4/54 (7.4%) at 121–179 $\mu\text{mol/L}$, to 19/56 (33.9%) at 180–210 $\mu\text{mol/L}$, and 31/48 (64.6%) at 211–310 $\mu\text{mol/L}$ (Cochran–Armitage $z = 6.07$, $p < 0.001$; **Figure 2**). Unequal category sizes resulted from tied concentrations at the tertile boundaries. Relative to the lowest category, unadjusted ORs were 6.42 (95% CI 2.01–20.45) and 22.79 (7.02–74.01). These wide intervals, particularly with only four events in the reference category, caution against treating the categorical effect sizes as precise.

The unadjusted OR per 10 $\mu\text{mol/L}$ uric acid was 1.45 (95% CI 1.27–1.65). In the five-predictor model it was 1.45 (1.24–1.69), while the metabolic-phenotype OR was 1.29 (0.52–3.22), compared with 3.69 (1.81–7.52) unadjusted (Table 4). This attenuation is compatible with shared information or confounding, but does not establish that uric acid mediates the phenotype association. The adjusted phenotype interval remains compatible with potentially important associations in either direction.

The exploratory model containing uric acid, BMI, HOMA-IR and age yielded a uric acid OR of 1.40 per 10 $\mu\text{mol/L}$ (95% CI 1.20–1.62). The BMI and HOMA-IR estimates were imprecise and not statistically significant. In the full model, variance inflation factors ranged from 1.01 to 1.31, and the Hosmer–Lemeshow statistic was 9.21 (8 degrees of freedom, $p = 0.325$). These findings did not identify substantial collinearity or lack of fit, but neither test establishes adequate performance in a new cohort. Quadratic and interaction assessments are reported with the model results.

Adding a quadratic uric acid term to the full model gave a likelihood-ratio statistic of 0.92 ($p = 0.337$). Separate full-model interaction tests gave $p = 0.323$, 0.475, 0.300 for phenotype, embryo stage and embryo number, respectively. No statistically detectable departure was identified; limited power remains a concern.

The adjusted embryo-stage OR was 1.57 (95% CI 0.46–5.39), which does not demonstrate equivalent risks for cleavage-stage and blastocyst transfers. Two-embryo transfer was associated with higher adjusted odds (OR 3.69, 95% CI 1.28–10.64), based on 23 exposed pregnancies and 12 composite events. This exploratory association is susceptible to confounding, multiplicity and selection on singleton delivery. Unrecorded vanishing twins provide another possible explanation. It should not determine transfer policy on its own.

3.5 Secondary outcome models

In the exploratory pre-eclampsia model, uric acid remained associated with the outcome after adjustment for phenotype (OR 1.45 per 10 $\mu\text{mol/L}$, 95% CI 1.22–1.71), while the phenotype estimate was 0.78 (0.24–2.55). In the gestational-diabetes analysis of 156 eligible women, phenotype was associated with recorded GDM (OR 3.84, 95% CI 1.48–9.95; $p = 0.006$), while the uric acid estimate was 1.05 (0.94–1.18; $p = 0.387$). These models suggest differing patterns of association. A significant coefficient for one outcome and a non-significant coefficient for another do not, by themselves, establish that the underlying effects differ. The models were not formal tests of separate biological pathways.

3.6 Discrimination and internal validation

Uric acid alone had an apparent ROC area of 0.809 (95% CI 0.738–0.881), compared with 0.697 for BMI, 0.586 for HOMA-IR and 0.693 for the uric acid/creatinine ratio. The five-predictor model had an apparent area of 0.824 (0.755–0.892; **Figure 3**). The difference between the multivariable model and uric acid alone was 0.014 (–0.019 to 0.048; $p = 0.402$). Because the model was developed and assessed in the same data, this apparent comparison should not be interpreted as a definitive test of incremental prognostic value. Bootstrap refitting yielded mean optimism of 0.021 and an optimism-corrected model area of 0.802 (Table 5). The uric acid-only area describes the discrimination of the observed marker; it does not validate a clinical prediction rule.

At the internally selected threshold of $\geq 192 \mu\text{mol/L}$, sensitivity was 47/54 (87.0%), specificity 69/104 (66.3%), positive predictive value 47/82 (57.3%) and negative predictive value 69/76 (90.8%). The positive and negative likelihood ratios were 2.59 and 0.20. The 2.5th–97.5th percentiles of bootstrap thresholds were 189–221 $\mu\text{mol/L}$. Predictive-value intervals and the other operating characteristics are conditional on the chosen threshold. They do not account for its selection in the same cohort. Seven composite events occurred below the threshold, and the results do not justify using uric acid alone to exclude placental disease or reduce antenatal surveillance.

3.7 Sensitivity analyses

Figure 4 displays the principal unadjusted and adjusted estimates. The uric acid association persisted across the specified restricted and additional-covariate models, with ORs ranging approximately from 1.38 to 1.45 per 10 $\mu\text{mol/L}$ (Table 5). Excluding the six women with uncertain aspirin timing left 152 women and 51 events; the OR was 1.42 (95% CI 1.22–1.65). Excluding women with chronic hypertension, pregestational diabetes or previous pre-eclampsia left 138 women and 42 events; the OR was 1.38 (1.18–1.61).

Creatinine adjustment produced an OR of 1.42 (95% CI 1.23–1.65) for uric acid. A single creatinine value is an incomplete measure of renal handling, so persistence after adjustment does not exclude renal confounding or haemoconcentration. Similarly, adjustment for one treatment characteristic cannot account for all differences in endometrial preparation. Within-phenotype uric acid ORs were 1.36 (1.15–1.60) in the phenotype group and 1.60 (1.18–2.16) in the comparison group. The limited subgroup event counts preclude a strong claim about differential effects.

3.8 Biological interpretation and relevance

These observations are consistent with a relationship between early uric acid and later placental complications, but do not distinguish a causal contribution from a correlated physiological signal. Reduced renal clearance, insulin resistance, vascular adaptation and other unmeasured factors could produce overlapping associations. The corpus luteum hypothesis is biologically plausible in view of previous cardiovascular studies (von Versen-Höynck et al., 2019; Conrad et al., 2022), yet this cohort contained no ovulatory-FET comparison group and did not measure relaxin, plasma volume or endothelial function. The data therefore cannot establish a mechanism specific to corpus luteum absence.

Prior observational work supports further investigation of early uric acid while cautioning against direct transport of estimates. Colmenares-Mejia et al. (2023) reported a pooled OR of 1.46 for the highest versus lowest uric acid quartile in prospective studies sampling before 20 weeks. Yue et al. (2023) examined an association with pre-eclampsia in an early-pregnancy cohort, and Laughon et al. (2011) likewise reported an association with subsequent pre-eclampsia. Our tertile contrasts are not directly comparable with those estimates because exposure scaling, adjustment, populations and endpoints differ. In particular, the present composite includes a Doppler-based component as well as clinical disease.

Uric acid metabolism also connects with natural-compound research. Lin et al. (2015) demonstrated structure-dependent inhibition of xanthine oxidase by dietary flavonoids in experimental assays. Such findings provide a biochemical rationale for research, but enzyme inhibition does not establish maternal or fetal safety, effective in-vivo exposure, or prevention of pregnancy complications. We measured neither diet nor natural-product use and tested no urate-lowering intervention. The present association consequently cannot support recommending dietary supplements, herbal preparations or urate-lowering treatment during pregnancy.

3.9 Limitations and related work

The single-setting retrospective design, absence of a reconstructable screening denominator, and restriction to pregnancies reaching singleton delivery may introduce selection bias. Source-level measurement validity is not established by internally consistent spreadsheet calculations. Assay performance, fasting procedures, detailed glucose-tolerance results, clinical adjudication variables and Doppler timing were incompletely documented. The composite combines outcomes of unequal clinical significance, including a report-based Doppler endpoint susceptible to measurement and ascertainment differences. Outcome-assessor blinding could not be established.

All women had aspirin prescriptions, but variable dose, adherence and duration could still influence outcomes. Uniform prescription status does not remove treatment-related confounding or establish how results would differ without prophylaxis. Other potential confounders include parity, chronic disease, infertility characteristics, diet and socioeconomic factors; the limited event count restricted simultaneous adjustment. Baseline uric acid and metabolic measurements were made at similar times, preventing a reliable mediation analysis. No external validation, formal assessment of clinical net benefit or comparison with an established risk algorithm was performed. Apparent discrimination and a bootstrap correction do not establish clinical usefulness.

4 CONCLUSION

Within this cohort of singleton pregnancies after programmed FET, higher first-trimester uric acid was associated with metabolic phenotype and subsequent placental complications. Its association with the composite outcome persisted in the specified adjusted models, while the phenotype coefficient attenuated with substantial residual uncertainty. The GDM analysis also identified an association with metabolic phenotype. These results are observational and exploratory; they do not establish mediation, equivalence between transfer stages, or a clinical uric acid threshold. Prospective studies with documented assays

and outcome adjudication, ovulatory-cycle comparison groups and external validation are needed before clinical implementation or urate-lowering interventions are considered.

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AUTHOR CONTRIBUTIONS

Sevara Sh. Rakhmanova: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft. Makhira L. Saipova: Investigation, Data curation, Writing – review and editing. Feruza D. Karimova: Supervision, Methodology, Writing – review and editing. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

ETHICS STATEMENT

Approval was granted by the Institutional Ethics Committee of the Republican Perinatal Center (IEC/RPC/2022/01, protocol No. 01/2022, decision dated 12 January 2022). The study was conducted in accordance with the Declaration of Helsinki (2013 revision). Individual informed consent was waived for the retrospective analysis of de-identified records.

DATA AVAILABILITY

The participant-level dataset, data dictionary and study notes are provided in Supplementary File 1. Derived phenotype groups and outcome-specific analysis denominators follow the definitions in this manuscript; the original group column and the unfiltered GDM count should not be used as substitutes for those definitions.

DECLARATION OF AI ASSISTANCE

OpenAI ChatGPT (GPT-5.6 Sol) was used in September 2026 to assist with language editing, reference verification, statistical cross-checking and document formatting. No participant-level observations were generated, replaced or altered during this revision. The authors verified the reported analyses and references and retain full responsibility for the integrity, interpretation and final approval of the manuscript.

REFERENCES

- [1] Bainbridge, S.A., Roberts, J.M., 2008. Uric acid as a pathogenic factor in preeclampsia. *Placenta* 29 (Suppl A), S67–S72. <https://doi.org/10.1016/j.placenta.2007.11.001>
- [2] Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *Journal of the Royal Statistical Society Series B (Methodological)* 57, 289–300. <https://doi.org/10.1111/j.2517-6161.1995.tb02031.x>
- [3] Busnelli, A., Schirripa, I., Fedele, F., Bulfoni, A., Levi-Setti, P.E., 2022. Obstetric and perinatal outcomes following programmed compared to natural frozen-thawed embryo transfer cycles: a systematic review and meta-analysis. *Human Reproduction* 37, 1619–1641. <https://doi.org/10.1093/humrep/deac073>
- [4] Colmenares-Mejia, C.C., Quintero-Lesmes, D.C., Bautista-Niño, P.K., Guío, E., Paez, M.C., Beltrán, M., Williams, D., Gray, K.J., Casas, J.P., Serrano, N.C., 2023. Uric acid and risk of pre-eclampsia: results from a large case–control study and meta-analysis of prospective studies. *Scientific Reports* 13, 3018. <https://doi.org/10.1038/s41598-023-29651-4>
- [5] Conrad, K.P., von Versen-Höynck, F., Baker, V.L., 2022. Potential role of the corpus luteum in maternal cardiovascular adaptation to pregnancy and preeclampsia risk. *American Journal of Obstetrics and Gynecology* 226, 683–699. <https://doi.org/10.1016/j.ajog.2021.08.018>

- [6] DeLong, E.R., DeLong, D.M., Clarke-Pearson, D.L., 1988. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 44, 837–845. <https://doi.org/10.2307/2531595>
- [7] Facchini, F., Chen, Y.D., Hollenbeck, C.B., Reaven, G.M., 1991. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA* 266, 3008–3011. <https://doi.org/10.1001/jama.1991.03470210076036>
- [8] Ginström Ernstad, E., Wennerholm, U.-B., Khatibi, A., Petzold, M., Bergh, C., 2019. Neonatal and maternal outcome after frozen embryo transfer: increased risks in programmed cycles. *American Journal of Obstetrics and Gynecology* 221, 126.e1–126.e18. <https://doi.org/10.1016/j.ajog.2019.03.010>
- [9] Kanellis, J., Kang, D.-H., 2005. Uric acid as a mediator of endothelial dysfunction, inflammation, and vascular disease. *Seminars in Nephrology* 25, 39–42. <https://doi.org/10.1016/j.semnephrol.2004.09.007>
- [10] Khosla, U.M., Zharikov, S., Finch, J.L., Nakagawa, T., Roncal, C., Mu, W., Krotova, K., Block, E.R., Prabhakar, S., Johnson, R.J., 2005. Hyperuricemia induces endothelial dysfunction. *Kidney International* 67, 1739–1742. <https://doi.org/10.1111/j.1523-1755.2005.00273.x>
- [11] Laughon, S.K., Catov, J., Powers, R.W., Roberts, J.M., Gandley, R.E., 2011. First trimester uric acid and adverse pregnancy outcomes. *American Journal of Hypertension* 24, 489–495. <https://doi.org/10.1038/ajh.2010.262>
- [12] Laughon, S.K., Catov, J., Provins, T., Roberts, J.M., Gandley, R.E., 2009. Elevated first-trimester uric acid concentrations are associated with the development of gestational diabetes. *American Journal of Obstetrics and Gynecology* 201, 402.e1–402.e5. <https://doi.org/10.1016/j.ajog.2009.06.065>
- [13] Lin, S., Zhang, G., Liao, Y., Pan, J., Gong, D., 2015. Dietary flavonoids as xanthine oxidase inhibitors: structure–affinity and structure–activity relationships. *Journal of Agricultural and Food Chemistry* 63, 7784–7794. <https://doi.org/10.1021/acs.jafc.5b03386>
- [14] Magee, L.A., Brown, M.A., Hall, D.R., Gupte, S., Hennessy, A., Karumanchi, S.A., Kenny, L.C., McCarthy, F., Myers, J., Poon, L.C., Rana, S., Saito, S., Staff, A.C., Tsigas, E., von Dadelszen, P., 2022. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis and management recommendations for international practice. *Pregnancy Hypertension* 27, 148–169. <https://doi.org/10.1016/j.preghy.2021.09.008>
- [15] Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C., 1985. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 28, 412–419. <https://doi.org/10.1007/BF00280883>
- [16] Mazzali, M., Hughes, J., Kim, Y.G., Jefferson, J.A., Kang, D.-H., Gordon, K.L., Lan, H.Y., Kivlighn, S., Johnson, R.J., 2001. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension* 38, 1101–1106. <https://doi.org/10.1161/hy1101.092839>
- [17] Saito, K., Kuwahara, A., Ishikawa, T., Morisaki, N., Miyado, M., Miyado, K., Fukami, M., Miyasaka, N., Ishihara, O., Irahara, M., Saito, H., 2019. Endometrial preparation methods for frozen-thawed embryo transfer are associated with altered risks of hypertensive disorders of pregnancy, placenta accreta, and gestational diabetes mellitus. *Human Reproduction* 34, 1567–1575. <https://doi.org/10.1093/humrep/dez079>
- [18] US Preventive Services Task Force, 2021. Aspirin use to prevent preeclampsia and related morbidity and mortality: US Preventive Services Task Force recommendation statement. *JAMA* 326, 1186–1191. <https://doi.org/10.1001/jama.2021.14781>
- [19] von Elm, E., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C., Vandenbroucke, J.P., 2007. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLOS Medicine* 4, e296. <https://doi.org/10.1371/journal.pmed.0040296>
- [20] von Versen-Höynck, F., Schaub, A.M., Chi, Y.-Y., Chiu, K.-H., Liu, J., Lingis, M., Williams, R.S., Rhoton-Vlasak, A., Nichols, W.W., Fleischmann, R.R., Zhang, W., Winn, V.D., Segal, M.S., Conrad, K.P., Baker, V.L., 2019. Increased preeclampsia risk and reduced aortic compliance with in vitro fertilization cycles in the absence of a corpus luteum. *Hypertension* 73, 640–649. <https://doi.org/10.1161/HYPERTENSIONAHA.118.12043>
- [21] Yue, C., Ying, C., Li, X., 2023. Association of first trimester serum uric acid with preeclampsia: an observational cohort study with propensity score matching. *Hypertension Research* 46, 377–385. <https://doi.org/10.1038/s41440-022-01115-8>

- [22] Zaat, T.R., Kostova, E.B., Korsen, P., Showell, M.G., Mol, F., van Wely, M., 2023. Obstetric and neonatal outcomes after natural versus artificial cycle frozen embryo transfer and the role of luteal phase support: a systematic review and meta-analysis. *Human Reproduction Update* 29, 634–654. <https://doi.org/10.1093/humupd/dmad011>

FIGURE LEGENDS

Figure 1. First-trimester uric acid by metabolic phenotype (A), composite outcome (B) and embryo stage (C). Boxes indicate median and interquartile range; whiskers extend to the most extreme values within 1.5 interquartile ranges of the box. Points show individual observations. Two-sided Mann–Whitney U p values are unadjusted.

Figure 2. Composite outcome incidence across cohort-based uric acid tertile categories. Bars show percentages and Wilson 95% confidence intervals; labels show event counts and denominators. Ties were retained together, producing unequal category sizes. The Cochran–Armitage trend test uses scores 1, 2 and 3.

Figure 3. Apparent ROC curves for the composite outcome. Areas use DeLong 95% confidence intervals. The five-predictor model contains uric acid, phenotype, age, embryo stage and embryo number. The highlighted ≥ 192 $\mu\text{mol/L}$ threshold was selected in the same data and is not a validated clinical cut-off. Model optimism-corrected AUC was 0.802; the displayed curve is the apparent curve.

Figure 4. Unadjusted and adjusted odds ratios for the composite outcome with Wald 95% confidence intervals on a logarithmic scale. Adjusted estimates use the five-predictor model in 158 pregnancies with 54 events. All displayed intervals are calculated from the same coefficients as Table 4.

TABLES

Table 1A. Baseline maternal characteristics by metabolic phenotype.

Characteristic	Phenotype (n = 82)	No phenotype (n = 76)	p
Maternal age, years	34.0 (30.0–37.8)	34.0 (31.0–37.0)	0.784
Height, cm	164.1 (160.4–167.2)	162.8 (159.8–165.9)	0.320
Pre-pregnancy weight, kg	87.0 (78.7–94.5)	67.7 (62.3–72.9)	—
BMI, kg/m ²	32.6 (29.1–35.4)	25.7 (23.5–27.0)	—
HOMA-IR	3.5 (2.0–5.7)	1.7 (1.3–2.1)	—
Fasting insulin, $\mu\text{IU/mL}$	15.7 (9.4–26.2)	7.6 (5.9–9.4)	—
Fasting glucose, mmol/L	5.0 (4.7–5.2)	5.0 (4.7–5.2)	—
Gravidity	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.798
Duration of infertility, years	5.0 (3.0–7.0)	5.0 (3.0–6.0)	0.605
Obesity, BMI ≥ 30 kg/m ²	60/82 (73.2)	0/76 (0.0)	—
Insulin resistance, HOMA-IR ≥ 2.5	52/82 (63.4)	0/76 (0.0)	—
Nulliparity	48/82 (58.5)	38/76 (50.0)	0.282
PCOS	23/82 (28.0)	6/76 (7.9)	0.001

Characteristic	Phenotype (n = 82)	No phenotype (n = 76)	p
Chronic hypertension	2/82 (2.4)	1/76 (1.3)	1.000
Pregestational diabetes	2/82 (2.4)	0/76 (0.0)	0.498
Smoking	2/82 (2.4)	3/76 (3.9)	0.672
Previous pre-eclampsia	7/82 (8.5)	8/76 (10.5)	0.670
Previous SGA infant	4/82 (4.9)	4/76 (5.3)	1.000

Values are median (IQR) or n/N (%). Mann–Whitney U, Pearson chi-square or Fisher exact tests were used as specified in Methods. No inferential p values are given for phenotype-defining variables or their direct components. SGA, small for gestational age. All baseline p values are exploratory.

Table 1B. Biochemical and transfer characteristics by metabolic phenotype.

Characteristic	Phenotype (n = 82)	No phenotype (n = 76)	p
Uric acid, $\mu\text{mol/L}$	211.5 (191.0–233.5)	176.5 (163.0–193.0)	<0.001
Creatinine, $\mu\text{mol/L}$	68.0 (62.2–74.0)	56.0 (50.0–60.0)	<0.001
Uric acid/creatinine ratio	3.10 (2.70–3.81)	3.22 (2.90–3.71)	0.389
Sampling gestational age, decimal weeks	10.1 (9.1–10.7)	10.0 (9.3–11.4)	0.323
Oestradiol, mg/day	6.0 (4.0–6.0)	4.0 (2.0–4.0)	<0.001
Oestradiol duration, days	12.0 (11.0–13.0)	12.0 (11.0–13.0)	0.171
Progesterone, mg/day	400.0 (200.0–600.0)	400.0 (400.0–600.0)	0.592
Blastocyst transfer	73/82 (89.0)	66/76 (86.8)	0.673
Two embryos transferred	11/82 (13.4)	12/76 (15.8)	0.672

Values are median (IQR) or n/N (%). All continuous comparisons use Mann–Whitney U tests. Gestational ages in this table are decimal weeks, not weeks.days notation. Ratio is dimensionless because both concentrations use $\mu\text{mol/L}$.

Table 2. First-trimester uric acid by metabolic, outcome and transfer strata.

Stratum	Present median (IQR) n	Absent median (IQR) n	Location shift (95% CI)	Cliff's δ p
Metabolic phenotype	211.5 (191.0–233.5) n = 82	176.5 (163.0–193.0) n = 76	35.0 (25.0–45.0)	0.59 <0.001
Composite outcome	222.5 (197.0–248.2) n = 54	180.0 (164.8–200.0) n = 104	38.0 (28.0–50.0)	0.62 <0.001

Stratum	Present median (IQR) n	Absent median (IQR) n	Location shift (95% CI)	Cliff's δ p
Pre-eclampsia	236.0 (210.0–256.0) n = 26	188.0 (169.0–210.0) n = 132	46.0 (28.0–62.0)	0.61 <0.001
Gestational diabetes	210.5 (187.0–230.0) n = 36	189.0 (168.5–210.0) n = 120	19.0 (4.0–34.0)	0.29 0.008
Blastocyst versus cleavage	192.0 (169.0–222.5) n = 139	200.0 (184.5–212.5) n = 19	-7.0 (-21.0–7.0)	-0.11 0.422
Two versus one embryo	197.0 (176.5–210.0) n = 23	193.0 (169.5–224.5) n = 135	-1.0 (-15.0–12.0)	-0.03 0.846

Uric acid and location shifts are in $\mu\text{mol/L}$. “Present” refers to the first-named category. Location shifts are Hodges–Lehmann pairwise differences with percentile bootstrap CIs from 2000 resamples. They are not differences between the displayed sample medians. P values are two-sided Mann–Whitney U tests and are unadjusted. GDM excludes pregestational diabetes (156 women).

Table 3A. Binary pregnancy outcomes by metabolic phenotype.

Outcome	Phenotype n/N (%)	No phenotype n/N (%)	RR (95% CI)	P p adjusted
Composite outcome	39/82 (47.6)	15/76 (19.7)	2.41 (1.45–4.00)	<0.001 Primary
Gestational diabetes*	28/80 (35.0)	8/76 (10.5)	3.33 (1.62–6.83)	<0.001 0.005
Placental dysfunction	31/82 (37.8)	12/76 (15.8)	2.39 (1.33–4.31)	0.002 0.010
Abnormal uteroplacental Doppler	27/82 (32.9)	9/76 (11.8)	2.78 (1.40–5.53)	0.002 0.010
Pre-eclampsia	19/82 (23.2)	7/76 (9.2)	2.52 (1.12–5.65)	0.018 0.052
Macrosomia ≥ 4000 g	14/82 (17.1)	4/76 (5.3)	3.24 (1.12–9.42)	0.020 0.052
Intrauterine fetal hypoxia	19/82 (23.2)	7/76 (9.2)	2.52 (1.12–5.65)	0.018 0.052
Preterm birth <37 weeks	18/82 (22.0)	7/76 (9.2)	2.38 (1.05–5.39)	0.028 0.065
Any hypertensive disorder	23/82 (28.0)	11/76 (14.5)	1.94 (1.01–3.70)	0.038 0.068

Outcome	Phenotype n/N (%)	No phenotype n/N (%)	RR (95% CI)	P p adjusted
Intrapartum fetal distress	14/82 (17.1)	5/76 (6.6)	2.60 (0.98–6.86)	0.043 0.068
Early neonatal complication	12/82 (14.6)	4/76 (5.3)	2.78 (0.94–8.25)	0.051 0.074
Low birth weight <2500 g	11/82 (13.4)	4/76 (5.3)	2.55 (0.85–7.66)	0.081 0.102
Apgar <7 at 1 minute	14/82 (17.1)	6/76 (7.9)	2.16 (0.88–5.34)	0.083 0.102
NICU admission	12/82 (14.6)	5/76 (6.6)	2.22 (0.82–6.02)	0.103 0.117
Gestational hypertension	4/82 (4.9)	4/76 (5.3)	0.93 (0.24–3.58)	1.000 1.000
Placental abruption	4/82 (4.9)	2/76 (2.6)	1.85 (0.35–9.83)	0.683 0.728
Caesarean delivery	39/82 (47.6)	24/76 (31.6)	1.51 (1.01–2.25)	0.040 0.068

RR, risk ratio, with Katz log-scale 95% CI. Raw p values use Pearson chi-square except Fisher exact tests for gestational hypertension and abruption. Adjusted p values use Benjamini–Hochberg correction across all 16 secondary binary comparisons, including caesarean delivery. The primary composite is excluded from this family. *Both women with pregestational diabetes are excluded from GDM comparisons (80 versus 76 women).

Table 3B. Continuous delivery and neonatal measurements by metabolic phenotype.

Measurement	Phenotype (n = 82)	No phenotype (n = 76)	Location shift (95% CI)	P
Gestational age at delivery, weeks	38.2 (37.0–39.1)	38.4 (37.6–39.1)	-0.3 (-0.8–0.1)	0.188
Birth weight, g	3512.5 (2888.0–3961.8)	3253.0 (2875.5–3456.0)	228.0 (27.0–419.0)	0.026
Blood loss, mL	470.0 (340.0–607.5)	380.0 (290.0–545.0)	60.0 (10.0–120.0)	0.034
Uterine artery PI	1.93 (1.55–2.22)	1.73 (1.45–1.98)	0.17 (0.05–0.28)	0.009
Umbilical artery PI	1.03 (0.92–1.15)	0.97 (0.85–1.10)	0.04 (-0.01–0.10)	0.149
Apgar score at 1 minute	8.0 (7.0–9.0)	8.0 (7.0–8.0)	0.0 (0.0–1.0)	0.388
Apgar score at 5 minutes	9.0 (8.0–10.0)	9.0 (9.0–10.0)	0.0 (0.0–0.0)	0.879

Values are median (IQR). Location shifts use Hodges–Lehmann estimates and percentile bootstrap CIs (2000 resamples). P values are exploratory, two-sided Mann–Whitney U tests without multiplicity correction. PI, pulsatility index; gestational-age information for the Doppler measurements is unavailable. Apgar scores are bounded ordinal measurements.

Table 4A. Logistic regression for the composite outcome.

Model and predictor	OR	95% CI	p
Model 1 UA alone			
Uric acid per 10 $\mu\text{mol/L}$	1.45	1.27–1.65	<0.001
Model 2 UA and phenotype			
Uric acid per 10 $\mu\text{mol/L}$	1.42	1.23–1.64	<0.001
Metabolic phenotype	1.28	0.53–3.09	0.577
Model 3 Five-predictor model			
Uric acid per 10 $\mu\text{mol/L}$	1.45	1.24–1.69	<0.001
Metabolic phenotype	1.29	0.52–3.22	0.581
Age per year	1.01	0.93–1.10	0.865
Blastocyst versus cleavage	1.57	0.46–5.39	0.472
Two versus one embryo	3.69	1.28–10.64	0.016
Model 4 Continuous metabolic markers			
Uric acid per 10 $\mu\text{mol/L}$	1.40	1.20–1.62	<0.001
HOMA-IR per unit	1.14	0.93–1.40	0.219
BMI per kg/m^2	1.02	0.93–1.13	0.644
Age per year	1.00	0.92–1.08	0.904
Unadjusted phenotype			
Metabolic phenotype	3.69	1.81–7.52	<0.001
Unadjusted uric acid categories			
180–210 versus 121–179 $\mu\text{mol/L}$	6.42	2.01–20.45	0.002
211–310 versus 121–179 $\mu\text{mol/L}$	22.79	7.02–74.01	<0.001

All models use 158 pregnancies and 54 events. Phenotype reference is absence; embryo-stage reference is cleavage-stage transfer; embryo-number reference is one embryo. Confidence intervals are Wald intervals. Model 3 contains five slope parameters. Uric acid categories are unadjusted. ORs should not be interpreted as risk ratios.

Table 4B. Exploratory models for pre-eclampsia and gestational diabetes.

Outcome and predictor	OR	95% CI	p
Pre-eclampsia; n (events) = 158 (26)			
Uric acid per 10 $\mu\text{mol/L}$	1.45	1.22–1.71	<0.001
Metabolic phenotype	0.78	0.24–2.55	0.682
Gestational diabetes; n (events) = 156 (36)			
Uric acid per 10 $\mu\text{mol/L}$	1.05	0.94–1.18	0.387
Metabolic phenotype	3.84	1.48–9.95	0.006

Each model contains uric acid and metabolic phenotype only. GDM analyses exclude pregestational diabetes. These p values are not adjusted for multiplicity and do not formally test whether associations differ between outcomes.

For reproducibility, the fitted Model 3 logit is $-9.180673 + 0.372484 \times (\text{uric acid}/10) + 0.256802 \times \text{phenotype} + 0.007244 \times \text{age} + 0.452030 \times \text{blastocyst} + 1.305893 \times \text{two embryos}$. Binary indicators are 1 when present and 0 otherwise; uric acid is in $\mu\text{mol/L}$ and age in years. This equation is not externally validated.

Table 5A. Discrimination for the composite outcome.

Marker or model	AUC	95% CI
Uric acid alone	0.809	0.738–0.881
Five-predictor model	0.824	0.755–0.892
BMI	0.697	0.611–0.784
HOMA-IR	0.586	0.483–0.688
Uric acid/creatinine ratio	0.693	0.608–0.777
Model 3 optimism-corrected AUC	0.802	Not estimated

AUC, area under the ROC curve. DeLong intervals refer to apparent areas. Bootstrap model optimism was 0.021; the correction used 993 estimable fits from 1000 attempted resamples (seven non-estimable fits excluded). The apparent model CI is not a CI for its optimism-corrected performance.

Table 5B. Exploratory paired AUC comparisons.

Comparison	Difference	95% CI	p
Uric acid minus BMI	0.112	0.032 to 0.192	0.006
Uric acid minus HOMA-IR	0.223	0.103 to 0.344	<0.001
Uric acid minus ratio	0.117	0.037 to 0.196	0.004
Model 3 minus uric acid	0.014	-0.019 to 0.048	0.402

Paired DeLong comparisons use the same participants. Model 3 comparisons use the score fitted in those participants and are descriptive apparent-performance comparisons. P values are unadjusted.

Table 5C. Apparent operating characteristics at uric acid ≥ 192 $\mu\text{mol/L}$.

Measure	Numerator / denominator	Percentage (95% CI)
Sensitivity	47/54	87.0 (75.1–94.6)
Specificity	69/104	66.3 (56.4–75.3)
Positive predictive value	47/82	57.3 (45.9–68.2)
Negative predictive value	69/76	90.8 (81.9–96.2)

Exact binomial CIs are conditional on this data-derived threshold and do not adjust for threshold selection. Bootstrap threshold percentiles were 189–221 $\mu\text{mol/L}$. Positive likelihood ratio 2.59; negative likelihood ratio 0.20.

Table 5D. Sensitivity and stratified analyses.

Analysis	n (events)	OR (95% CI)	p
Original group label	158 (54)	1.40 (1.21–1.61)	<0.001
Exclude chronic hypertension, pregestational diabetes or previous pre-eclampsia	138 (42)	1.38 (1.18–1.61)	<0.001
Exclude uncertain aspirin timing	152 (51)	1.42 (1.22–1.65)	<0.001
Single-embryo transfers	135 (42)	1.42 (1.21–1.67)	<0.001
Blastocyst transfers	139 (49)	1.39 (1.20–1.61)	<0.001
Add serum creatinine	158 (54)	1.42 (1.23–1.65)	<0.001
Add daily oestradiol dose	158 (54)	1.41 (1.22–1.64)	<0.001
Add PCOS	158 (54)	1.42 (1.23–1.65)	<0.001
Add sampling gestational age	158 (54)	1.45 (1.24–1.68)	<0.001
Uric acid/creatinine ratio per 0.1 unit	158 (54)	1.15 (1.07–1.22)	<0.001
Phenotype stratum	82 (39)	1.36 (1.15–1.60)	<0.001
No-phenotype stratum	76 (15)	1.60 (1.18–2.16)	0.002

Unless labelled as a ratio, estimates are per 10 $\mu\text{mol/L}$ uric acid. Sensitivity models contain uric acid and phenotype, with the stated change or one added covariate; they do not otherwise include the full-model covariates. Original-label analysis substitutes the stored group column for derived phenotype. Stratified models contain uric acid alone. All p values are exploratory.

FIGURES

Figure 1

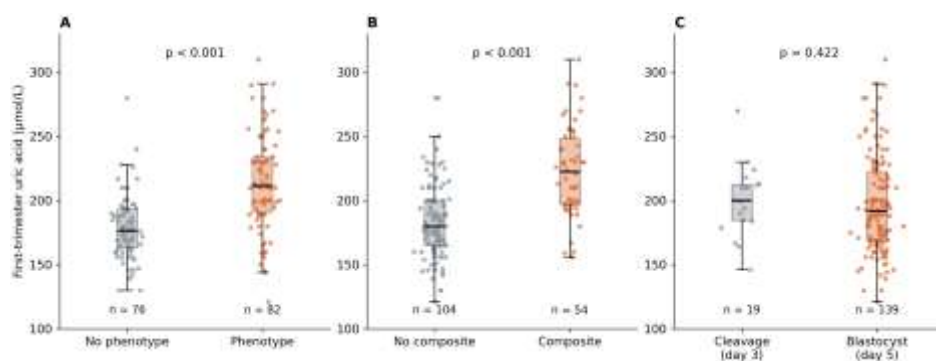


Figure 2

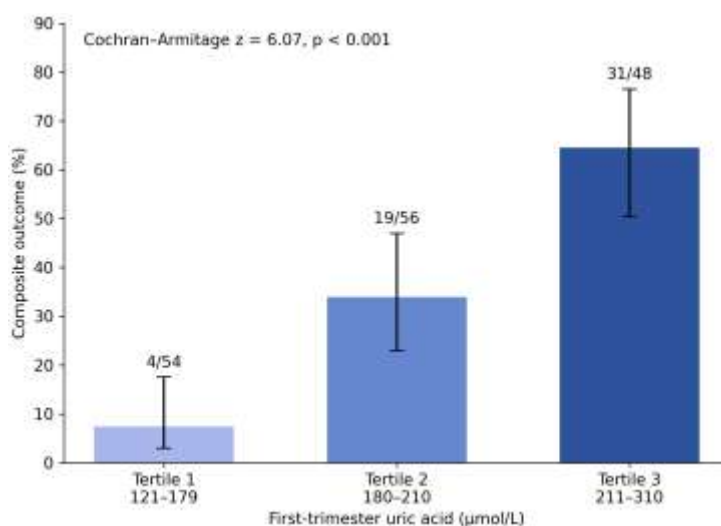


Figure 3

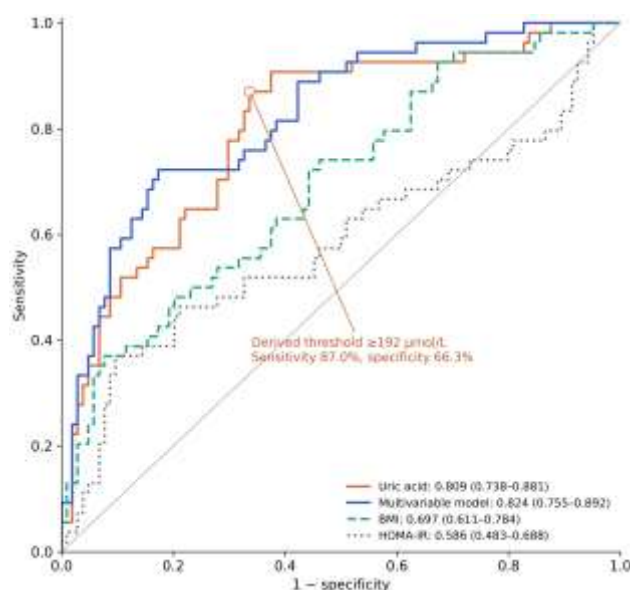


Figure 4

