

Corpus Luteum Absence Is an Independent Risk Factor for Early Pregnancy Loss After ART: A Risk Stratification Model with Temporal Validation

Huiyi Xie¹

Quanzhou Women and Children's Hospital

Yifang Wu¹

Quanzhou Women and Children's Hospital

Yunni Cai¹

Quanzhou Women and Children's Hospital

Jin'gu Li

antimui@vip.qq.com

Quanzhou Women and Children's Hospital

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Abstract

Background

To determine whether endometrial preparation protocols influence the risk of early pregnancy loss after assisted reproductive technology (ART) through corpus luteum (CL)-dependent mechanisms, and to assess the feasibility of integrating CL status as an independent predictor in a multivariable risk stratification model.

Methods

This single-center retrospective cohort study screened 6485 cycles achieving clinical pregnancy after IVF/ICSI or FET between 2012 and 2026. After excluding ongoing pregnancies (448), losses to follow-up (78), and ectopic pregnancies (94), 5865 cycles with definitive outcomes (live birth or spontaneous abortion) were analyzed. Cycles were classified by the presence of an endogenous CL into a CL-present group (fresh embryo transfer and FET natural cycle) and a CL-absent group (FET-HRT and FET-GnRHa + HRT). The 2012–2022 data formed the training set ($n = 3582$); the 2022–2026 data formed the independent temporal validation set ($n = 2283$).

Results

After excluding ectopic pregnancies, loss rates showed a clear gradient consistent with the CL hypothesis. The two CL-present groups had the lowest and comparable rates (fresh embryo transfer 14.9%; FET natural cycle 13.3%; $P = 0.689$). The two CL-absent FET groups were significantly higher (FET-GnRHa + HRT 18.9%; FET-HRT 19.8%; four-group $\chi^2 P = < 0.001$). The pooled CL+ group (14.8%) differed from the CL- group (19.4%) by 4.6 percentage points ($P = < 0.001$). After multivariable adjustment, CL absence remained an independent risk factor (aOR = 1.128, 95% CI 1.029–1.236, $P = 0.010$), but the cryopreservation effect could not be fully separated because the FET natural cycle subgroup was small ($n = 143$). The 7-variable model achieved an AUC of 0.6464 in independent temporal validation, significantly outperforming age alone (AUC = 0.6011, $\Delta\text{AUC} = 0.0453$, DeLong $P < 0.001$), with a risk gradient from 3.2% to 39.1% (12-fold).

Conclusions

Fresh embryo transfer and FET natural cycle (both with an endogenous CL) had the lowest and comparable loss rates. CL absence was an independent risk factor for pregnancy loss, but the independent effect of cryopreservation could not be fully separated because of the limited FET natural cycle sample. The 7-variable risk stratification model effectively distinguished four risk tiers and significantly outperformed age alone.

Background

Frozen embryo transfer (FET) now accounts for a substantial and rising proportion of global ART cycles^[1]. Three endometrial preparation protocols are used: natural cycle (NC), hormone replacement therapy (HRT), and GnRH agonist downregulation + HRT (GnRHa + HRT). These protocols differ fundamentally in whether an endogenous corpus luteum (CL) is present^[2]. NC involves ovulation and therefore has a functional CL. HRT and GnRHa + HRT both use exogenous estrogen and progesterone without ovulation, and therefore lack a CL. Fresh IVF/ICSI cycles invariably form a CL after oocyte retrieval, making all fresh embryo transfers CL-present. This CL distinction has clinical significance: a network meta-analysis showed that CL-present letrozole-stimulated cycles had significantly lower miscarriage rates than CL-absent HRT protocols (OR 0.59)^[3]. Thus, the difference in CL status determined by the endometrial preparation protocol may represent a key, yet underappreciated, factor in pregnancy loss risk stratification.

Multiple large-scale studies have consistently linked HRT-FET to higher rates of adverse perinatal outcomes — preeclampsia, postpartum hemorrhage, large-for-gestational-age infants, and preterm birth^[4–7]. The likely mechanism is impaired placental vascular remodeling caused by deficiency of CL-derived vasoactive factors such as relaxin^[8]. The 2025 ESHRE guideline^[9] and a concurrent Cochrane review^[10] both recommend natural cycle or ovarian stimulation cycles over HRT-FET when medically feasible. A 2023 clinical practice review by Zhang et al. on FET endometrial preparation updated the evidence base for CL-dependent mechanisms^[2]. In China, however, HRT protocols still account for over 60% of FET cycles^[11], largely because of scheduling flexibility. Nordic scholars have questioned whether this practice is driven by workflow convenience rather than evidence^[12]. Asian population-specific data on how endometrial preparation protocols affect pregnancy loss risk remain scarce. Globally, pregnancy loss affects ~ 15% of clinical pregnancies^[13], with risk rising steeply with age. Arkfeld et al. analyzed 66,793 ART cycles from the SART CORS database and showed that low AMH (< 1 ng/mL) independently predicts miscarriage in patients without PMOS (OR 1.2, 95% CI 1.1–1.3)^[14], suggesting that ovarian reserve markers may contribute to risk stratification.

The corpus luteum hypothesis offers a biological explanation for these clinical observations. The CL is critical for maintaining early pregnancy^[15]: CL-derived relaxin, VEGF, and renin-angiotensin system factors^[16–18] promote spiral artery remodeling and placental angiogenesis. When these vasoactive factors are absent — as in CL-absent protocols — placentation may be impaired, raising the risk of early pregnancy loss. As noted above, the network meta-analysis by Zeng et al. also showed that CL-present cycles had significantly lower miscarriage rates than CL-absent HRT protocols^[3]. The CL hypothesis therefore offers a unifying biological framework for the pregnancy loss risk differences across endometrial preparation protocols.

No empirical study has yet incorporated CL status as an independent predictor in a multivariable risk model. Clinical risk assessment still relies mainly on age and prior miscarriage history. Existing ART

pregnancy loss or live-birth prediction models are largely restricted to a single ART modality and almost never include endometrial preparation protocol ^[19,20] or CL status ^[21] as predictors. More importantly, nearly all use internal cross-validation without independent temporal validation, so their true generalizability remains untested ^[22]. Our center performs several thousand ART cycles annually – representative of most centers in China and globally. A simple model that integrates CL status for pre-treatment risk stratification, even with an AUC improvement of only 0.04–0.05, could provide more accurate individualized counseling for hundreds of couples each year and offer evidence-based guidance for FET protocol selection (NC vs. HRT).

Using 5865 ART pregnancies from our center, this study addresses these gaps with two objectives: (1) to validate the CL hypothesis at the whole-ART-cycle level, comparing pregnancy loss risk across fresh ET (CL-present), FET-NC (CL-present), and CL-absent FET protocols (HRT, GnRHa + HRT); and (2) to develop and temporally validate a 7-variable risk stratification model that integrates CL status with routine clinical factors. The core innovation is elevating CL status from a qualitative grouping variable to an independently quantifiable predictor in a multivariable model, with generalizability assessed through rigorous temporal validation (2012–2022 training, 2022–2026 validation).

Methods

Study design and data source

This was a single-center retrospective cohort study. We screened cycles achieving clinical pregnancy after IVF/ICSI or FET at the Reproductive Medicine Center of Quanzhou Women's and Children's Hospital during 2012–2026. After excluding ongoing pregnancies (448, not yet reaching an outcome by the study cutoff), losses to follow-up (78), and ectopic pregnancies (94), 5865 cycles with definitive outcomes were analyzed. The temporal split used June 30, 2022 as the cutoff: data from September 2012 to June 2022 formed the training set ($n = 3582$), and data from July 2022 to March 2026 formed the independent temporal validation set ($n = 2283$).

Outcome definition

The primary outcome was pregnancy loss: spontaneous abortion after clinical pregnancy (ultrasound-confirmed intrauterine gestation), without live birth ($n = 1028$). Live birth was the reference outcome ($n = 4837$). Ectopic pregnancies ($n = 94$) were excluded from the primary analysis because their pathogenesis (tubal factors) differs from endometrial-embryo interaction failure, and were reported separately. Biochemical pregnancies (β -hCG positive, no gestational sac visualized) were not analyzed independently because reliable retrospective ascertainment is difficult (addressed in Discussion).

Corpus luteum status definition and model variables

Cycles were classified by endogenous CL presence: (1) CL-present: fresh IVF/ICSI (CL from oocyte retrieval) + FET-NC (CL from ovulation) + FET with ovulation induction (small sample, grouped here); (2) CL-absent (no corpus luteum): FET-HRT + FET-GnRHa + HRT (both use exogenous estrogen and progesterone without ovulation, so no CL). Model A, the primary model, included seven routinely available variables: age, AMH, BMI, infertility duration, no corpus luteum, multiple gestational sacs (> 1), and prior spontaneous abortion (0–3). A 5-variable compact model (Model B, excluding BMI and prior SA) was evaluated in sensitivity analyses. The correlation matrix of the seven predictors is shown in Supplementary Figure S1 (no strong collinearity among variables).

Missing data handling and model validation

Missing data (primarily AMH, 42.3%) were handled by multiple imputation using chained equations (MICE, $m = 20$) [23]. AMH missingness showed a marked temporal gradient: near-complete absence in 2012–2016 (99.6%), declining to 52.4% in 2017–2019 and 21.5% in 2023–2026, reflecting the gradual adoption of AMH testing in Chinese reproductive medicine. The missingness pattern for each variable is shown in Supplementary Figure S2. The 2012–2022 data formed the training set ($n = 3582$); the 2022–2026 data formed the independent temporal validation set ($n = 2283$). The primary model used logistic regression. Coefficients were pooled across MICE imputations with Rubin's rules and internally validated by 200 bootstrap resamples. Discrimination was assessed by AUC. Incremental value over age alone was evaluated by the DeLong test, continuous NRI, and IDI. Calibration was assessed by calibration curves and the Brier score; clinical net benefit by decision curve analysis. Because individual-level calibration was suboptimal, the model is positioned as a risk stratification tool rather than an individual probability predictor.

Results

Study population

Baseline characteristics differed significantly between the loss and live birth groups. A total of 5865 pregnancy cycles with definitive outcomes were analyzed (Table 1): 2406 fresh ET (41%) and 3459 FET (59%). Live birth occurred in 4837 cycles (82.5%); pregnancy loss in 1028 cycles (17.5%, all spontaneous abortions). An additional 94 ectopic pregnancies were excluded. The loss group was significantly older (33.4 ± 4.5 vs. 31.6 ± 4.0 years, $P < 0.001$) and had lower AMH (median 3.0 vs. 3.4 ng/mL).

Table 1 Baseline characteristics of the live birth and pregnancy loss groups

Characteristic	Live birth (n=4837)	Pregnancy loss (n=1028)	P
Age (years)	31.6±4.0	33.4±4.5	<0.001
BMI (kg/m ²)	22.2±3.1	22.5±3.2	0.001
AMH (ng/mL)	3.4 [2.2–5.2]	3.0 [1.7–4.6]	<0.001
Infertility duration (years)	3.8±2.9	4.3±3.1	<0.001
Cycle type (Fresh/FET)	2048/2789	358/670	<0.001

Table 1 Continuous variables are presented as mean ± SD or median [IQR]. *P* values from Mann-Whitney U test (continuous) or χ^2 test (categorical).

Corpus luteum absence independently increases pregnancy loss risk: an ART-wide gradient

After stratifying all cycles by CL status and cryopreservation, loss rates showed a gradient fully consistent with the CL hypothesis (Fig. 1). The two CL-present groups had the lowest rates: fresh ET (CL+, no cryo) 14.9% (2406 cycles) and FET-NC (CL+, with cryo) 13.3% (143 cycles) were comparable ($P=0.689$). The two CL-absent groups were significantly higher: FET-GnRHa+HRT (CL-, cryo) 18.9% (1375 cycles) and FET-HRT (CL-, cryo) 19.8% (1909 cycles) did not differ from each other ($P=0.553$). Both CL-absent protocols differed significantly from fresh cycles (vs. FET-HRT $P<0.001$; vs. FET-GnRHa+HRT $P=0.001$). The four-group trend was highly significant ($\chi^2=22.15$, $df=3$, $P<0.001$). Pooling into CL+ (fresh + FET-NC, $n=2549$, 14.8%) and CL- (FET-GnRHa+HRT + FET-HRT, $n=3284$, 19.4%) yielded a difference of 4.6 percentage points ($\chi^2=21.15$, $P<0.001$). Importantly, fresh and FET cycles differ in both CL status and cryopreservation exposure. FET-NC – the only subgroup with both a CL and cryopreservation – comprised only 143 cycles. This provides insufficient power to cleanly separate the cryopreservation effect from the CL effect (discussed further below).

Age-stratified analysis reinforced this gradient. Among women <35 years, fresh ET loss rates (12.3%) were significantly lower than HRT (16.2%). Among women ≥35 years, age became dominant and between-protocol differences were attenuated. However, FET-NC in this subgroup comprised only 45 cycles, too few to detect meaningful protocol differences. Wide confidence intervals reflect substantial selection bias: older women with regular ovulation who are eligible for NC-FET systematically differ in ovarian reserve and endocrine status from age-matched HRT users. Pregnancy loss rates across clinical subgroups (age, cycle type, BMI, AMH, transfer type, pregnancy type, embryo quality, period, oocyte yield, and FET protocol) are shown in Supplementary Table S1. In sum, the CL gradient was robust among younger women but attenuated by age in older women.

Age is the strongest independent predictor of pregnancy loss

Age was the strongest independent predictor. Loss rates rose monotonically with age (<30: 12.0%; 30–34: 15.8%; 35–37: 21.3%; 38–40: 25.1%; ≥40: 46.4%). Age and AMH showed an interaction: younger women (<35) with high AMH had the lowest loss rate (14.0%); older women (≥35) with low AMH had the highest (28.9%), a difference of 14.9 percentage points. In sum, the combined age-by-AMH stratification produced a clear loss rate gradient.

Embryo morphology adds no independent predictive value: the "ceiling effect" of clinical pre-screening

Unexpectedly, embryo morphology had little effect on loss risk once clinical pregnancy was established. In FET cycles, all transferred embryos had morphological grading. Loss rates for good-quality embryos (18.8%) and non-good-quality embryos (20.0%) were similar (χ^2 $P=0.438$). Among blastocyst transfers, loss rates were likewise comparable for good (17.4%) and poor (19.7%) quality embryos. This is not coincidental. Embryo quality primarily affects implantation — good-quality embryos yield higher clinical pregnancy rates — not post-implantation maintenance. Once implantation succeeds and a gestational sac is visible, embryo morphology has limited ability to predict whether the pregnancy will reach live birth. At this stage, maternal factors (age, CL status, uterine environment) become the dominant determinants of outcome. Adding embryo quality to the 5-variable baseline model in the independent validation set improved the AUC by only 0.0213, supporting this interpretation.

The 7-variable model significantly outperforms age alone: Δ AUC +0.045 (DeLong $P<0.001$)

The 7-variable logistic regression model (Model A, Table 2) achieved an internal AUC of 0.6743 ± 0.0246 in the training set under 5×10 -fold repeated cross-validation. This is an optimistic estimate because training and validation data are from the same period. In the independent temporal validation set (2022–2026, unseen during training), the AUC was 0.6464 (Brier score 0.1474), providing an unbiased estimate of generalizability to future patients. The gap between internal and validation AUC ($\Delta=0.0279$) was expected and reflects temporal distributional drift. The model significantly outperformed age alone (AUC=0.6011, Δ AUC=0.0453, DeLong $P<0.001$; NRI=0.2236, IDI=0.033), showing that the six additional variables add clinically meaningful discrimination beyond age. CL absence was an independent predictor (aOR=1.128, 95% CI 1.029–1.236, $P=0.010$), providing multivariable-adjusted evidence for the CL hypothesis. Model A outperformed the 5-variable compact model (Model B, AUC=0.6276, Δ AUC=0.0188), supporting the 7-variable specification as optimal (predictor contributions shown in Fig. 2). Sensitivity

analyses (complete-case analysis, cross-validation on 2022–2026 data) and Model A/B/C comparisons are shown in Supplementary Tables S2 and S3.

Table 2 Multivariable logistic regression results (Model A, 7 variables)

Predictor	aOR	95% CI	P
Age (per year)	1.386	1.261–1.524	<0.001
Multiple sacs (vs singleton)	0.699	0.639–0.765	<0.001
Prior spontaneous abortion	1.263	1.160–1.374	<0.001
AMH (per ng/mL)	0.910	0.832–0.995	0.038
Infertility duration (per year)	1.122	1.021–1.233	0.017
No corpus luteum (vs has CL)	1.128	1.029–1.236	0.010
BMI (per kg/m²)	1.092	0.996–1.196	0.060

Table 2 aOR = adjusted odds ratio. Coefficients pooled via MICE with Rubin's rules and internally validated by 200 bootstrap resamples.

The model classifies patients into four risk tiers, with a 12-fold gradient in observed loss rates

Based on predicted probabilities, patients were classified into four risk tiers (Table 3): low (<10%, n=95, observed 3.2%), moderate (10–20%, n=1363, observed 15.2%), high (20–30%, n=546, observed 20.7%), and very high (>30%, n=279, observed 39.1%). Observed loss rates between the low- and very-high-risk groups differed by ~12-fold, demonstrating clear discriminative capacity at the group level. Individual-level calibration, however, was suboptimal (calibration slope = 3.6629, Fig. 3). We therefore position this model as a risk stratification tool – identifying which risk tier a patient belongs to, not predicting her exact loss probability.

Table 3 Risk stratification performance (temporal validation set, n=2283)

Risk group	n	Predicted mean probability	Observed loss rate
Low risk (<10%)	95	9.3%	3.2%
Moderate risk (10–20%)	1363	14.9%	15.2%
High risk (20–30%)	546	24.2%	20.7%
Very high risk (>30%)	279	43.8%	39.1%

Table 3 Predicted probabilities were recalibrated via logistic regression.

Discussion

Whole-ART-cycle validation of the corpus luteum hypothesis

The core finding of this study is the validation and quantification of the CL hypothesis at the whole-ART-cycle level. Stratifying cycles by CL status and cryopreservation revealed a loss rate gradient fully consistent with the hypothesis: the two CL-present groups had the lowest and mutually comparable rates, the two CL-absent FET groups were significantly higher and also comparable, and the pooled CL+ versus CL- comparison was highly significant. This complete gradient – CL-present protocols consistently outperforming CL-absent ones across all ART types – has not been systematically reported before.

As shown in the Results, fresh ET and FET-NC had comparable loss rates, directionally consistent with the multicenter RCT of Shi et al. [24]. This apparent equivalence, however, carries two caveats. First, fresh and FET cycles differ in cryopreservation exposure. Both have a CL, but only FET undergoes freezing and thawing. In principle, the cryopreservation effect should be isolated by comparing FET-NC (CL+, cryo) against FET-HRT (CL-, cryo). Yet FET-NC comprised only 143 cycles, and the difference from FET-HRT did not reach statistical significance ($P = 0.073$). An independent cryopreservation contribution cannot be excluded. Second, the Fresh vs. FET-NC equivalence test had only ~ 8% power. If the true FET-NC loss rate equals that of fresh ET, roughly 500 NC cycles would be needed for 80% power to detect a 5-percentage-point difference. Thus, the current data cannot distinguish a true null from a real difference rendered non-significant by inadequate sample size. Nonetheless, the rank order across all four groups is fully consistent with the CL hypothesis, and CL absence remained an independent risk factor after adjustment – the most rigorous quantitative evidence to date for this hypothesis.

GnRHa + HRT loss rates fell between NC and pure HRT, suggesting that pituitary downregulation may partially offset CL absence. Possible mechanisms include suppression of endogenous LH fluctuations, reduction of local endometrial inflammation, and optimization of the implantation window [25]. Age-stratified analysis suggested possible effect modification: the CL gradient was clear among women < 35 years, but among those ≥ 35 years none of the three protocol comparisons reached significance (all $P > 0.4$). The older NC subgroup had wide confidence intervals, reflecting substantial selection bias: older women with regular ovulation who are eligible for NC-FET systematically differ from age-matched HRT users in ovarian reserve and endocrine status.

Preserving endogenous corpus luteum function should be central to FET protocol selection

These findings have direct clinical implications. First, for ovulatory FET patients, NC protocols should be prioritized to preserve endogenous CL function. This aligns with the 2025 ESHRE guideline^[9] and a meta-analysis of PMOS-related complications^[26]. Second, when HRT is required (e.g., anovulation or PMOS), GnRHa + HRT should be preferred over pure HRT, especially in older patients where the advantage is more pronounced. PMOS patients show elevated miscarriage risk during FET cycles, particularly the hyperandrogenic phenotype^[27]. HRT protocols currently account for > 60% of FET cycles in China^[11], largely for workflow convenience rather than medical indication. Given that both our data and the 2025 network meta-analysis^[3] link CL-absent protocols with higher pregnancy loss risk, this practice pattern warrants reconsideration. In sum, preserving endogenous CL function should be a central consideration in FET protocol selection.

Moderate AUC but a clear risk gradient supports clinical decision-making value

All seven variables in Model A are routinely collected, imposing no additional testing burden. The model's moderate AUC in independent validation is not a fatal limitation: it provides a clear risk gradient for clinical decisions and significantly outperforms age alone. This level of discrimination falls within the expected range for pregnancy loss prediction — population-based live-birth prediction models built on UK national IVF registry data^[19,28] similarly showed moderate discrimination, and a recent multicenter Chinese IVF miscarriage model achieved an external-validation AUC of 0.615^[20]. A substantial share of pregnancy loss is attributable to embryonic aneuploidy and other stochastic events beyond the reach of clinical variables^[29]. We recommend tiered intensified monitoring for high- and very-high-risk patients: enhanced luteal support, early serial β -hCG and progesterone monitoring, and more frequent early ultrasound. In sum, Model A offers an optimal balance between parsimony and discrimination, supporting its use as a clinical decision aid.

The "protective effect" of multiple sacs reflects collider bias, not causality

Multiple gestational sacs were associated with lower loss rates, but this apparent protective effect requires caution. First, our outcome definition creates an inherent bias: loss is defined at the cycle level. If at least one sac yields a live birth, the cycle is classified as live birth. Multiple sacs thus raise the probability that at least one survives. For example, in a vanishing twin scenario — one sac is lost early while the other survives — the cycle is counted as a live birth. Had only the lost embryo been transferred, it would be a definitive pregnancy loss. Second, embryos capable of dual-sac implantation possess inherently higher developmental potential — a collider bias^[30], not a causal protective effect of multiplicity. This should not be misinterpreted as evidence that transferring more embryos reduces loss risk. The age-by-AMH interaction — lowest loss in young, high-AMH women; highest in older, low-AMH women — suggests that ovarian quantity and quality jointly influence pregnancy maintenance. Future models might incorporate an age $\times$ AMH interaction term. In sum, the multiple-sac association likely reflects embryo intrinsic quality and outcome-definition bias rather than a causal protective effect.

Strengths and limitations

Strengths of this study include: (1) first integration of CL status as an independent predictor in a multivariable model spanning both IVF/ICSI and FET, providing whole-ART-cycle evidence for the CL hypothesis; (2) a large sample (n = 5865) with rigorous temporal validation offering a genuine test of generalizability; (3) all seven predictors are routine clinical variables, facilitating external validation. Limitations include: (1) Single-center retrospective design. FET protocol selection is subject to confounding by indication. Multivariable adjustment and age stratification reduce but cannot eliminate unmeasured confounding. (2) Fresh and FET cycles differ by both CL status and cryopreservation. FET-NC, the only subgroup that can isolate the cryopreservation effect, comprised only 143 cycles — too few for adequate power. This is the core methodological limitation in testing the CL hypothesis. Future studies require a large NC-FET cohort (~ 500 cycles) to cleanly separate cryopreservation from CL effects. (3) AMH missingness showed a temporal gradient (2012–2016: 99.6%; 2017–2019: 52.4%; 2023–2026: 21.5%). MICE imputation assumes missing at random. Early-period AMH was almost entirely absent because routine AMH testing had not yet been adopted in China. This missingness is conditional on time. Imputed values reflect period-specific means, but selective AMH testing in suspected diminished ovarian reserve cannot be excluded. The model should preferentially be applied to patients with measured AMH. (4) PGT-A data were unavailable, yet embryonic aneuploidy is the single most important biological cause of early miscarriage^[29]. In sum, this study provides the largest quantitative evidence to date for the CL hypothesis, but future multicenter prospective designs are needed to confirm causality and further improve model performance.

Conclusion

In a large ART pregnancy cohort, the two CL-present groups (fresh ET and FET-NC) had the lowest and comparable loss rates. The two CL-absent FET groups showed significantly higher rates. CL absence was an independent risk factor. The independent cryopreservation contribution could not be fully isolated because the FET-NC subgroup was underpowered — the core methodological question for future research. The 7-variable model effectively classified patients into four risk tiers, significantly outperforming age alone.

The main limitations are confounding by indication in the single-center retrospective design and near-complete absence of AMH data before 2016, which required imputation-based extrapolation. Future multicenter prospective studies and stepped-wedge trials are needed to verify the causal link between CL-absent protocols and pregnancy loss. Incorporating PGT-A data and more comprehensive reproductive history may further improve model discrimination and calibration.

Abbreviations

ART
assisted reproductive technology

AUC
area under the receiver operating characteristic curve
aOR
adjusted odds ratio
BMI
body mass index
AMH
anti-Müllerian hormone
CI
confidence interval
CL
corpus luteum
CPR
clinical pregnancy rate
DCA
decision curve analysis
eSET
elective single embryo transfer
FET
frozen embryo transfer
Gn
gonadotropin
HRT
hormone replacement therapy
ICSI
intracytoplasmic sperm injection
IVF
in vitro fertilization
LR
logistic regression
MICE
multiple imputation by chained equations
NC
natural cycle
OR
odds ratio
PPOS
progesterin-primed ovarian stimulation
ROC
receiver operating characteristic

SA
spontaneous abortion
SMD
standardized mean difference.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Quanzhou Women's and Children's Hospital (approval no. 2024 – 133) and complies with the ethical principles of the Declaration of Helsinki. As a retrospective cohort study, the requirement for informed consent was waived by the Ethics Committee.

Consent for publication

All patients provided broad informed consent before their prior IVF/ICSI treatment, authorizing the use of de-identified medical records for retrospective research. As this was a retrospective study, additional informed consent was waived.

Competing interests

All authors declare no competing interests.

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Author Contribution

H.Y.X. conceived the study design, performed the data analysis, and drafted the manuscript. Y.F.W. participated in data collection and quality control. Y.N.C. participated in data extraction and literature search. J.G.L., as corresponding author, supervised the study, provided clinical guidance, and finalized the manuscript. All authors read and approved the final manuscript.

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DeepSeek (DeepSeek-V4-Pro) was used as a writing and language-editing aid during the preparation of this manuscript. All academic viewpoints, data analysis, and conclusions were independently completed and are the responsibility of the authors.

Data Availability

The data supporting the findings of this study are contained within the article and its supplementary information files. Because of patient privacy and hospital data management regulations, individual patient data are not publicly available, but can be obtained from the corresponding author upon reasonable request and after approval by the institutional review board.

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Figures

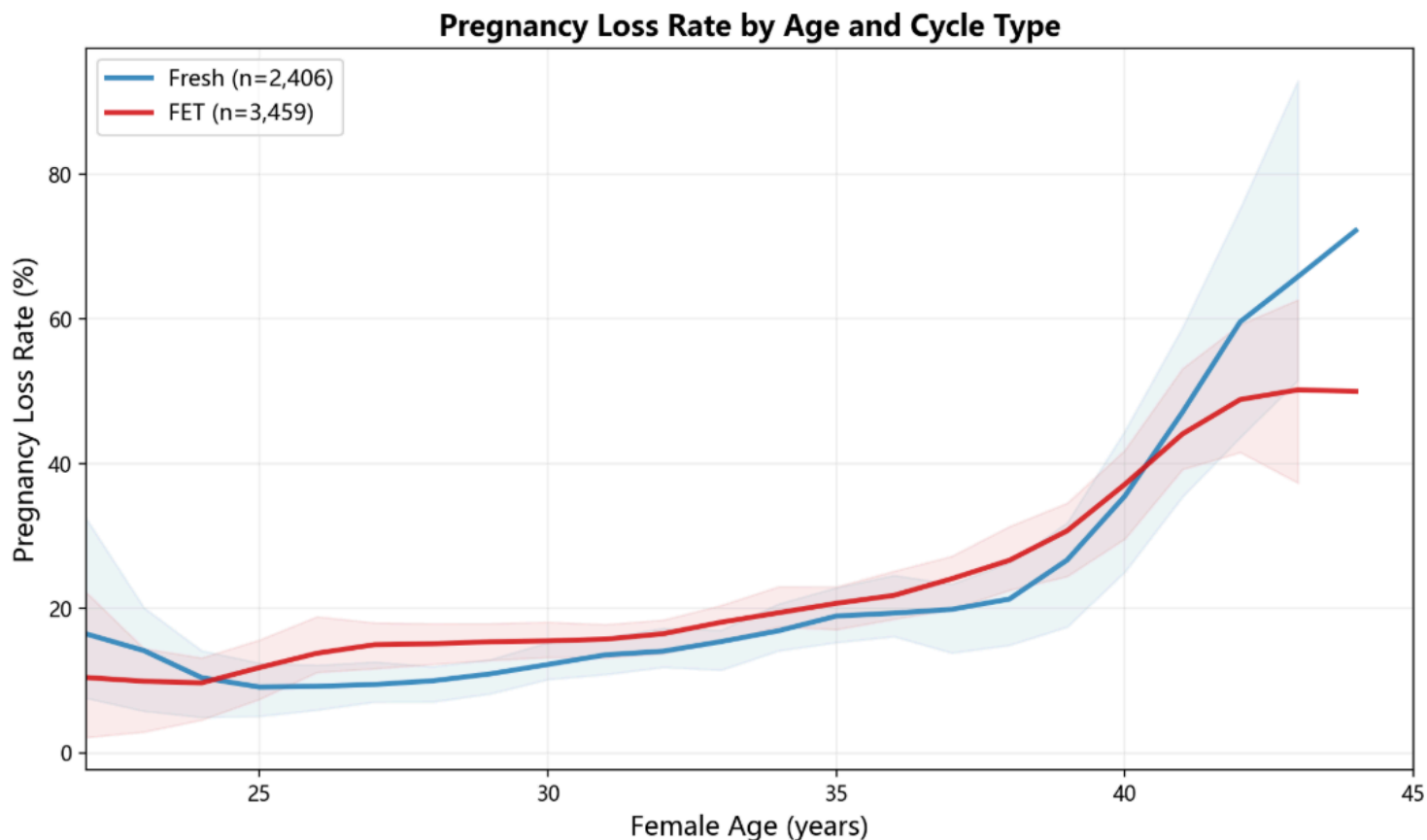


Figure 1

Age-stratified pregnancy loss rates by cycle type.

Shaded areas represent 95% confidence intervals. CL-present protocols (fresh ET and FET-NC) show consistently lower loss rates across all age strata than CL-absent FET protocols.

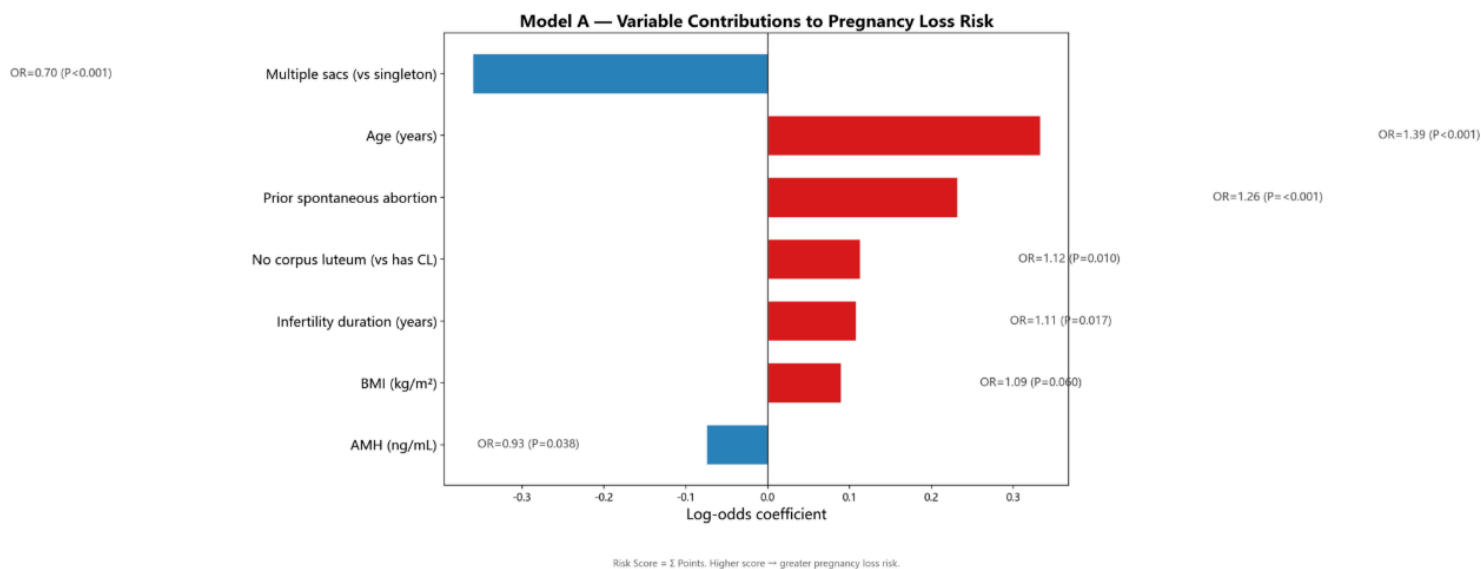


Figure 2

Predictor contribution plot (Model A, 7 variables)

Red bars denote risk factors (positive coefficients); blue bars denote protective factors (negative coefficients). OR values annotated beside each bar.

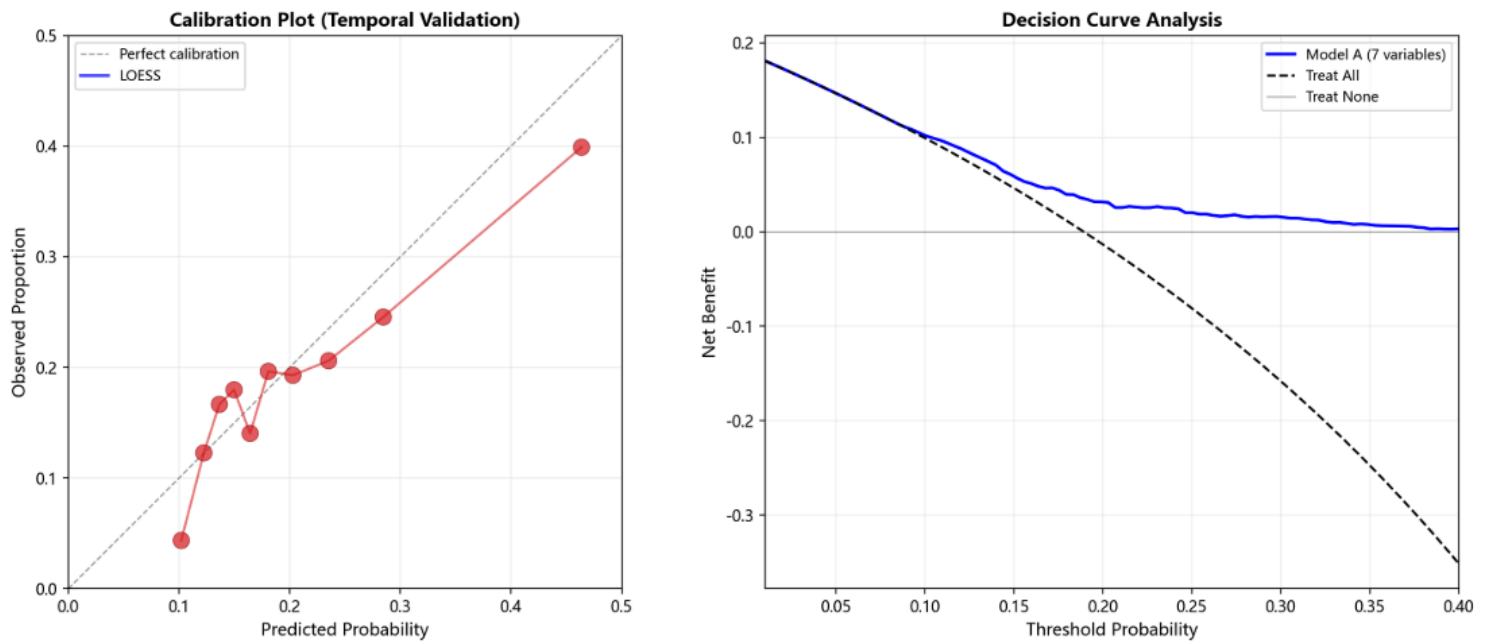


Figure 3

Calibration curve and decision curve analysis

Left: predicted probability vs. observed proportion; dashed line indicates perfect calibration. Right: net benefit across different risk thresholds.

Supplementary Files

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- [SupplementaryMaterial.docx](#)