OPEN ACCESS

COMMENTARY

The Innovation Medicine

Reaffirming the role of ovarian reserve in fertility assessment: Insights from OvaRePred

Huiyu Xu,[1,2,3,4,6] Guoshuang Feng,[5,6] Rui Yang,[1,2,3,4,6] Rong Li,[1,2,3,4,*] and Jie Qiao[1,2,3,4,*]

[1]State Key Laboratory of Female Fertility Promotion, Center for Reproductive Medicine, Department of Obstetrics and Gynecology, Peking University Third Hospital, Beijing 100191, China

[2]Key Laboratory of Assisted Reproduction, Ministry of Education, Beijing 100191, China

[3]National Clinical Research Center for Obstetrics and Gynecology, Beijing 100191, China

[4]Beijing Key Laboratory of Reproductive Endocrinology and Assisted Reproductive Technology, Beijing 100191, China

[5]Big Data Center, Beijing Children's Hospital, Capital Medical University, National Center for Children's Health, Beijing 100045, China

[6]These authors contributed equally

*Correspondence: roseli001@bjmu.edu.cn (R.L.); jie.qiao@263.net (J.Q.)

Received: January 2, 2025; Accepted: May 8, 2025; Published Online: May 9, 2025; https://doi.org/10.59717/j.xinn-med.2025.100135

Citation: Xu H., Feng G., Yang R., et al. (2025). Reaffirming the role of ovarian reserve in fertility assessment: Insights from OvaRePred. *The Innovation Medicine* **3**:100135.

In a recent JAMA study, Steiner et al.[1] investigated the association between ovarian reserve biomarkers —such as Anti-Müllerian Hormone (AMH), Follicle-Stimulating Hormone (FSH), and inhibin B —and natural fertility among late-reproductive-age women. The study included 981 women aged 30–44 who had no history of infertility and had been trying to conceive for less than 3 months. The authors found that low AMH or high FSH levels were not associated with significantly reduced fecundability or lower cumulative probabilities of conception over 6 or 12 cycles compared to women with normal levels. Essentially, the study does not support using FSH or AMH levels in urine or blood as standalone indicators of natural fertility.

One significant limitation of the study is its reliance on dichotomizing continuous biomarker values into binary categories —classifying ovarian reserve as simply "low" or "normal" based on set cutoffs. This approach is overly simplistic, as it may obscure the subtle, continuous variability of ovarian reserve and its gradual impact on fertility. Consequently, this raises the question of whether a more integrative approach—such as a composite measure like the OvaRePred tool (http://121.43.113.123:9999/)[2]—could provide a more accurate and clinically meaningful assessment of ovarian reserve and fertility. The Ovarian reserve score here is calculated based on previously developed AA model (AMH and age). It calculates an individual's poor ovarian response probability (POR probability) to derive an ovarian reserve score (i.e., 100×[1−POR probability]). At the same time, the tool utilizes an ovarian aging curve constructed from a large sample dataset—using a logistic growth model to describe the relationship between the predicted diminished ovarian reserve (DOR) proportion and age —to match the current ovarian reserve status with a specific future ovarian reserve value (for example, the starting age of perimenopause corresponds to the lowest ovarian reserve score in the assisted reproduction population). This approach allows us to estimate the time interval needed to reach that critical value, thereby predicting the future onset age of perimenopause.[2] This AI-driven tool not only automates the integration of multiple ovarian reserve markers —rather than relying on a single biomarker —but also delivers fully quantitative, reproducible scores for current ovarian reserve and forecasts key fertility milestones. By removing manual interpretation and standardizing analyses, OvaRePred enhances objectivity, scalability, and precision in reproductive assessment. Building on this, we aim to investigate various infertile factors affecting fertility within an assisted reproductive technology (ART) context.

DATASET OF FIRST-CYCLE ART TREATMENT COHORT

Clinical pregnancy outcomes were followed through April 2023. We analyzed 22,360 ART cycles from patients undergoing their first treatment between 2017 and 2019 to identify which infertility factor most strongly influences cumulative clinical pregnancy rates. To avoid confounding from repeated ART interventions, only each patient's first treatment cycle was included. Using unique patient identifiers, we captured outcomes from all treatment cycles including both fresh cycles and subsequent frozen-thawed embryo transfer cycles linked to previous stimulation. After excluding cycles with incomplete data and those using donor sperm, 21,131 first-treatment cycles remained. We retained only one non-pregnancy cycle per patient and kept only the first successful pregnancy cycle if repeated clinical pregnancies exist within the span of years occurred. Basic demographic and cycle characteristics are detailed in Figure 1A. Statistical analyses were conducted using SAS JMP PRO 17.0, with significance set at $P < 0.05$. The definitions of different infertility factors and the various ovarian stimulation protocols are detailed in previously published articles.[3,4]

SCREENING FOR RISK FACTORS AFFECTING FERTILITY

Fertility, defined as a couple's ability to achieve clinical pregnancy,[5] was the basis for selecting clinical pregnancy as the outcome. We chose cumulative pregnancy rates rather than single-cycle pregnancies, due to the fact that many patients undergo multiple thawed embryo transfers in subsequent cycles. Focusing only on single-cycle pregnancies could exclude significant censored data.

Logistic regression with best subset method, determined by the Bayesian Information Criterion (BIC), were used to screen risk factors. As illustrated in Figure 1B, the BIC ceases to decrease with the inclusion of eight variables, thereby designating this configuration as the final model. The final model included eight variables: number of previous pregnancies, ovarian reserve score, ovarian stimulation protocols, tubal factors, duration of infertility, natural or stimulation cycles, uterine factors, and chromosomal abnormality. Figure 1C presents the odds ratio (OR) for each variable via a forest plot. For instance, after adjusting for other variables, having an ovarian reserve score of less than 25, compared to a score of 95 or higher, is associated with a 27.15-fold increased risk of infertility (not clinical pregnancy in our study period). The ORs for the remaining variables are also depicted in Figure 1C. Figure 1D demonstrates the variable importance, with ovarian reserve contributing over 80%, while other infertility factors each account for less than 5%. This suggests that ovarian reserve is the most critical factor affecting fertility among individuals attending ART center. Here, main effect reflects the relative contribution of each variable alone, and total effect reflects the relative contribution of each variable alone and in combination with others. It's important to note that the infertility factors discussed here were those documented in our reproductive center. Finally, Figure 1E offers a conceptual diagram of the ovarian reserve assessment and menopause prediction software.

LIMITATIONS

Our focus was to screening risk factors for infertility, acknowledging the complexity of fertility, influenced by a wide range of biological, physiological, and environmental factors. This study has other limitations, including the potential underestimation of factors like immune-related issues and elements affecting embryo quality or oocyte maturation. Additionally, due to the lack of data on certain factors, our study did not include risk factors such as smoking, alcohol use, and environmental pollution in this analysis. The study is also limited by its single-center scope, which may not fully represent

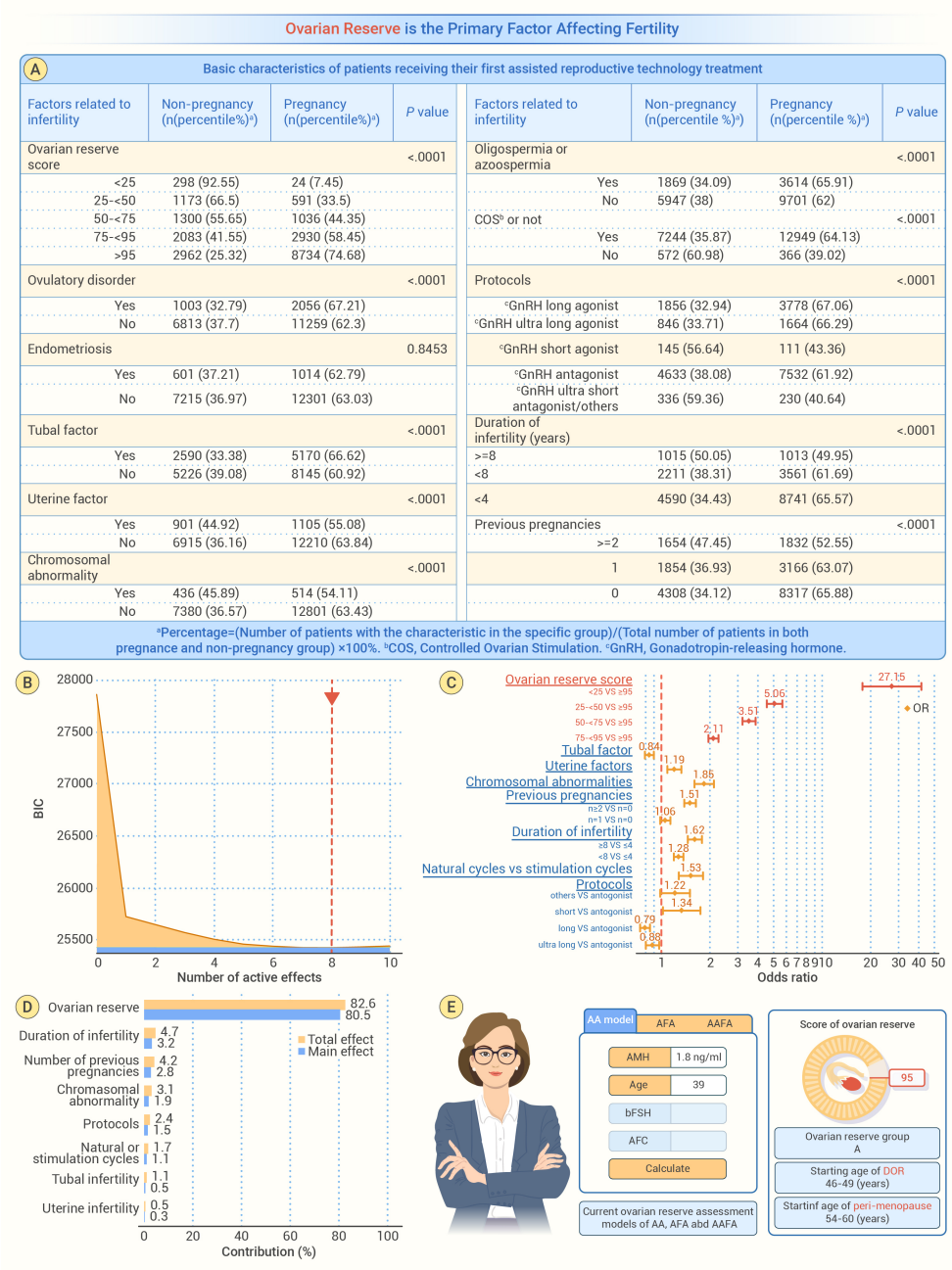

Figure 1. Ovarian Reserve as the Primary Driver of Fertility Outcomes in First - Cycle ART Cohort (A) Baseline characteristics of 21,131 first-treatment cycles stratified by non-pregnancy versus pregnancy, showing ovarian reserve score alongside other infertility factors, protocols and patient history. (B) Bayesian Information Criterion (BIC) as a function of the number of active effects included in multivariable modeling, with the optimal model indicated by the red dashed line. (C) Adjusted odds ratios (ORs) for each factor in the optimal model, demonstrating the dominant impact of ovarian reserve score on infertility (not clinical pregnancy in our study period). (D) Contribution of each predictor to model performance, highlighting ovarian reserve as the principal effect. (E) Conceptual workflow of the AA, AFA and AAFA AI models within the OvaRePred tool, mapping AMH, age, bFSH and AFC inputs to an individualized ovarian reserve score and predicted ages of diminished ovarian response (DOR) and perimenopause onset.

broader populations. Future research should consider a multi-center approach to gain a more comprehensive understanding and cover a wider demographic.

CONCLUSION

Fertility research endeavors to unravel and address the multifaceted challenges stemming from social, economic, and medical factors. The crucial role of ovarian reserve for fertility is evident, especially considering that menopause, depletion of ovarian reserve, signifying the complete cessation of fertility. However, what is often less known is the significant variation in ovarian reserve among individuals. Therefore, it is advisable for women of childbearing age to assess their ovarian reserve as early as possible to achieve a better balance between their career and family planning.

REFERENCES

1. Steiner A. Z., Pritchard D., Stanczyk F. Z., et al. (2017). Association between biomarkers of ovarian reserve and infertility among older women of reproductive age. *JAMA* **318**:1367–1376. DOI:10.1001/jama.2017.14588
2. Xu H. Y., Feng G. S., Yang R., et al. (2023). OvaRePred: Online tool for predicting the age of fertility milestones. *The Innovation* **4**:100490. DOI:10.1016/j.xinn.2023.100490
3. Xu H., Feng G., Wang H., et al. (2020). A novel mathematical model of true ovarian reserve assessment based on predicted probability of poor ovarian response: A retrospective cohort study. *J. Assist. Reprod. Genet.* **37**:963–972. DOI:10.1007/s10815-020-01700-1
4. Yang R., Zhang C., Chen L., et al. (2020). Cumulative live birth rate of low prognosis patients with POSEIDON stratification: A single-centre data analysis. *Reprod. Biomed. Online* **41**:834–844. DOI:10.1016/j.rbmo.2020.08.003
5. Zegers-Hochschild F., Adamson G. D., Dyer S., et al. (2017). The international glossary on infertility and fertility care, 2017. *Fertil. Steril.* **108**:393–406. DOI:10.1016/j.fertnstert.2017.06.005

FUNDING AND ACKNOWLEDGMENTS

This study was supported by National Key Research and Development Program of China (grant number 2023YFC2705500 and 2024YFC2706900); and the Innovation & Transfer Fund of Peking University Third Hospital (Grant No. BYSYZHKC2023102, and BYSYZHZB2020102). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

DECLARATION OF INTERESTS

Jie Qiao, Rong Li and Guoshuang Feng are Editorial Board members of The Innovation Medicine. They were not involved in the review or decision-making process for this manuscript. The article underwent the journal's standard procedures, with peer review handled independently of these Editorial Board members and their research groups. The other authors declare no competing interests.