International Journal of Reproduction, Contraception, Obstetrics and Gynecology
Selvaraj P et al. Int J Reprod Contracept Obstet Gynecol. 2026 Jun;15(6):2152-2157
www.ijrcog.org
pISSN 2320-1770 | eISSN 2320-1789

DOI: https://dx.doi.org/10.18203/2320-1770.ijrcog20261626

Original Research Article

Optimizing *in vitro* fertilization outcomes in non-receptive endometrium using combined histological dating and endometrial receptivity array: a retrospective study

Priya Selvaraj*, Kamala Selvaraj, Mahalakshmi Sivakumar, Sowmya Sudan, Kalaichelvi Srinivasan

Department of IVF, G. G. Hospital, Fertility Research and Women's Speciality Centre, Chennai, Tamil Nadu, India

Received: 16 April 2026
Accepted: 18 May 2026

***Correspondence:**
Dr. Priya Selvaraj,
E-mail: drpriya@gghospital.in

ABSTRACT

Background: Precise identification of the window of implantation (WOI) is crucial for optimizing embryo transfer and improving assisted reproductive technology (ART) outcomes. While the endometrial receptivity array (ERA) evaluates molecular receptivity, histological endometrial dating is a simpler, cost-effective alternative. However, comparative evidence is limited. This study assessed concordance between ERA and histological dating and evaluated whether their combined use improves outcomes in patients with non-receptive endometrium.
Methods: This retrospective study included 886 women undergoing ART between January 2021 and December 2025. Patients were categorized as ERA-receptive (n=562) or ERA non-receptive (n=324). Among non-receptive patients, outcomes were compared between those who underwent histological endometrial biopsy (EB) and those who did not. Subgroup analysis was conducted based on histological phase (proliferative versus secretory). Primary outcomes included clinical pregnancy, implantation, live birth, miscarriage, and ongoing pregnancy rates.
Results: ERA-receptive patients showed significantly higher clinical pregnancy and implantation rates compared to non-receptive patients. Within the non-receptive group, histological evaluation was associated with improved clinical pregnancy (38.38% versus 23.02%), implantation (17.99% versus 9.73%), and live birth rates (31.82% versus 15.08%). Secretory-phase endometrium demonstrated superior clinical pregnancy (44.53% versus 24.59%) and live birth rates (40.15% versus 13.11%) compared to proliferative phase.
Conclusions: Both ERA and histological dating are associated with improved ART outcomes. Histological assessment provides complementary value in ERA non-receptive patients. An integrated molecular and histological approach may enhance embryo transfer timing and improve reproductive success.

Keywords: Endometrial receptivity array, Histologic dating, Window of implantation, Endometrial receptivity, Assisted reproductive technology

INTRODUCTION

Successful embryo implantation requires on a competent blastocyst, a receptive endometrium, and an intricate dialogue between the embryo and maternal tissues.[1,2] Post-implantation embryo survival is determined not only by the embryo's intrinsic developmental potential but also by the degree of endometrial receptivity at or near the time of embryo transfer. Despite advancements in assisted reproductive technology (ART), including optimized ovarian stimulation, enhanced embryo culture techniques, preimplantation genetic screening, and measures of endometrial receptivity, the implantation rates remain suboptimal. Precise identification of the window of implantation (WOI) remains essential for optimizing embryo transfer timing and improving live birth outcomes in ART cycles.

Approximately 20% of infertile women and up to 25% of those with recurrent implantation failure (RIF) have been reported to exhibit a non-receptive endometrium.[3] In patients with RIF following *in vitro* fertilization (IVF), evaluation of endometrium during the mid-luteal phase is often performed using histologic or transcriptomic methods. Histologic assessment of endometrial biopsies (EB) based on the Noyes criteria helps determine whether endometrial morphology corresponds to the expected window of receptivity. In addition, it offers a cost-effective, widely accessible tool to identify timing discrepancies in endometrial maturation for personalized embryo transfer (pET). Furthermore, it allows direct evaluation of other pathologies associated with infertility, including tuberculosis, endometritis, and endometrial hyperplasia. However, histological evaluation is inherently limited by interobserver variability, represents a single static snapshot of endometrial status, and may lack precision in accurately delineating the WOI.[1]

Today, histologic dating has been largely replaced by endometrial receptivity array (ERA) to optimize the timing of embryo transfer by classifying the endometrium as receptive or non-receptive based on the expression of 248 genes involved in endometrial maturation during the WOI.[4] Despite its proposed role in optimizing endometrial receptivity, recent studies has shown no significant difference in live birth rates between standard-timed frozen embryo transfer and ERA-guided pET. These findings underscore the inconsistency of current evidence regarding the effectiveness of ERA in improving reproductive outcomes, even in cycles involving euploid embryo transfer.[3,5] Moreover, the cost and invasive nature of the ERA test remain important barriers, limiting its acceptance among patients with infertility.

In accordance with prior studies assessing endometrial receptivity, this retrospective study aimed to evaluate the concordance between histologic dating and ERA and to assess whether integrating these approaches could provide complementary insights to resolve discrepancies in endometrial receptivity. Additionally, the study sought to determine whether this integrated assessment could improve the precision of WOI identification, enabling a personalized approach to optimize implantation potential and ultimately improve reproductive outcomes in patients with non-receptive endometrium.

METHODS

Study design and setting

This retrospective study was conducted between January 2021 and December 2025 at GG Hospital, Fertility Research and Women's Speciality Centre, Chennai, India.

Study population

The study population consisted of 886 women with documented thin or poor endometrial lining, RIF, and unexplained pregnancy loss. All the patients were given oral and written information regarding the procedure and consents were taken for the same. Flowchart depicting the process of patient enrolment and eligibility assessment in the study are shown in figure1.

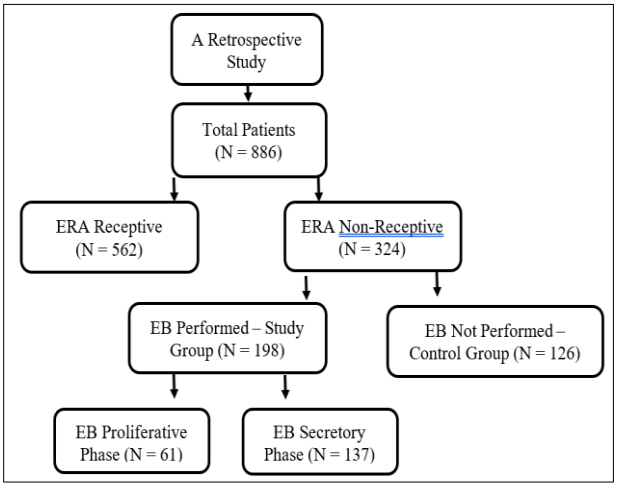

Figure 1: Flowchart illustrating the process of patient screening and eligibility assessment in the study evaluating the concordance between histological dating and ERA.

Inclusion criteria

Inclusion criteria involved participants with thin or poor endometrial lining (≤0.7 cm on transvaginal ultrasound during the peri-implantation period), history of RIF, defined as failure to achieve a clinical pregnancy after the transfer of at least two consecutive embryo transfers with morphologically high-quality blastocysts (Gardner Grading System) and history of unexplained pregnancy loss.[6]

Exclusion criteria

Women with uterine or endometrial conditions known to impair endometrial receptivity, cases involving euploid blastocyst transfers, and surrogacy cases were excluded.

The stimulation protocols employed for patients using self-gametes comprised of the long and short protocol based on factors such as age, previous reproductive outcomes, hormone values, quality and quantity of oocytes and embryos.

Endometrial receptivity analysis and histopathological evaluation

ERA was performed during a hormone replacement therapy (HRT) cycle. Incremental doses of estradiol valerate (2 mg) (Zydus Cadila, Sikkim, India) were administered from day 2/3 of the menstrual cycle until mid-cycle assessment on day 12/13, with a minimum daily dose of 6–8 mg increased up to a maximum of 12 mg

depending on endometrial response. On day 16, a trigger dose of human chorionic gonadotropin (hCG) 10,000 IU (Amlife, Gujarat, India) was administered along with initiation of vaginal micronized progesterone 400 mg. Subsequently, micronized progesterone was administered in both oral and vaginal forms at doses ranging from 800–1200 mg (Sun Pharmaceuticals, Gujarat, India). The first progesterone intake was designated as P+0, and endometrial biopsy was performed on P+5 (day 21).

Endometrial tissue was obtained transvaginally using an endometrial sampler (Probet) and transferred to a cryotube containing 1.5 ml RNA stabilizing agent (Igenomix, Delhi, India). Samples were stored at 4°C until shipment at room temperature to Igenomix, Spain, for transcriptomic analysis. ERA results were reported as receptive (R) or non-receptive (NR) based on proprietary analysis of the expression of 248 genes.

In parallel, an endometrial biopsy was obtained following the same HRT protocol and preserved in 10% formalin for histopathological examination at Neuberg Ehrlich Laboratory using hematoxylin and eosin staining. Findings were categorized as proliferative or secretory phase, based on morphological characteristics. ERA and EB were classified as 'concordant' when samples were receptive or non-receptive by both tests.

Personalized embryo transfer

Sequential embryo transfers involved cleavage-stage embryo transfer on P+3 followed by blastocyst transfer on P+5. Single embryo transfer consisted of either a cleavage-stage embryo on P+3 or a blastocyst on P+5, according to the individualized ERA and EB profile. All the personalized embryo transfer decisions were based on the ERA result. The primary outcomes were then measured as clinical pregnancy rate, implantation rate, miscarriage rate, live birth rate and ongoing pregnancy rate.

Descriptive statistics were used to summarize patient demographics and baseline clinical characteristics. Continuous variables with a normal distribution are presented as mean±standard deviation (SD) and were compared using the independent samples t-test. Categorical variables are expressed as frequencies and proportions and were analysed using the chi-square test or Fisher's exact test, as appropriate. Pregnancy rates and other clinical outcomes were assessed using suitable statistical methods. All statistical tests were two-tailed, and a $p<0.05$ was considered statistically significant. Statistical package for the social sciences (SPSS) version 12.0 was used for statistical analysis.

RESULTS

Study population

A total of 886 patients were included in the analysis, of whom 562 (63.4%) displayed an ERA-receptive endometrium and the remaining 324 (36.6%) exhibited an ERA-non-receptive endometrium.

Comparison of baseline characteristics and pregnancy outcomes in patients with ERA-receptive and ERA non-receptive endometrium

Baseline demographic and clinical characteristics, including age, duration of infertility, endometrial thickness, number of previous failed embryo transfers, and number of embryos transferred, were comparable between the two groups, with no statistically significant differences observed (Table 1).

Notably, clinical outcomes were significantly improved in the ERA-receptive group. The clinical pregnancy rate was higher in the receptive group compared to the non-receptive group (47.69% versus 32.41%; $p<0.001$). Similarly, implantation rates were higher in the receptive group (22.46% versus 14.77%; $p<0.001$). The live birth rate was also markedly higher in patients with a receptive endometrium (38.26% versus 25.31%; $p<0.001$), along with a higher ongoing pregnancy rate (4.98% versus 0.62%; $p<0.001$). Conversely, miscarriage rates were lower in the receptive group (4.45% versus 6.48%), and no ectopic pregnancies were observed, compared to a small proportion (0.62%) in the non-receptive group.

Comparison of baseline characteristics and pregnancy outcomes in ERA non-receptive patients with and without histologic dating of endometrial biopsy

We stratified 324 ERA non-receptive patients into two subgroups based on whether histologic dating of EB was performed. Accordingly, 198 patients underwent EB, while 126 did not. Baseline demographic and clinical characteristics were broadly comparable between these two subgroups. Within the ERA non-receptive cohort, EB performance was associated with markedly improved reproductive outcomes (Table 2).

Clinical pregnancy rates were significantly higher when EB was performed vs control group within the ERA non-receptive group (38.38% versus 23.02%; P 0.0058). In parallel, implantation rates were substantially improved following EB (17.99% [84/467] versus 9.73% [29/298]; $p=0.0024$). Live birth rates also favoured the EB performed group, with nearly a twofold increase observed compared to patients without endometrial biopsy (31.82% versus 15.08%; 0.0012) (Table 3).

Correlation analysis between histologic phases of endometrial biopsy and reproductive outcomes in ERA non-receptive patients

Among ERA non-receptive patients who underwent histologic EB, outcomes were further stratified based on biopsy phase (proliferative phase, N=61 versus secretory phase, N=137). A statistically significant association was observed between histologic endometrial phase and

reproductive outcomes, highlighting its clinical relevance in influencing implantation success. Clinical pregnancy rates were significantly higher in patients with secretory phase endometrium compared with those in the proliferative phase (44.53% versus 24.59%; p=0.0122). In line with this, implantation rates were also markedly improved in the secretory phase group (20.49% [67/327] versus 12.14% [17/140]; p=0.0434). Live birth outcomes demonstrated a strong positive correlation with secretory phase histology, with rates nearly threefold higher than in the proliferative phase group (40.15% versus 13.11%; p=0.0003). Conversely, miscarriage rates were lower in the secretory phase cohort (4.38% versus 11.48%). The clinical pregnancy rate was comparable between ERA-receptive and secretory-phase endometrium in patients with ERA non-receptive endometrium, with no statistically significant difference observed (47.69% versus 44.53%). Overall, this study suggests that the histologic phase of the endometrium is positively correlated with reproductive outcomes, with secretory-phase endometrium showing a significant association with improved implantation rates and higher live birth rates in patients with ERA non-receptive endometrium (Table 4).

Table 1: Demographics characteristics and clinical outcomes in patients with ERA receptive and non-receptive endometrium.

Baseline parameters	ERA receptive	ERA non-receptive	P value	Significance
No. of patients	562	324		
Mean female age (years) ±SD	34.32±4.92	34.60±4.18	0.38	NS
Mean duration of Infertility (years) ±SD	8.80±4.26	8.30±4.25	0.09	NS
Primary infertility (%)	319 (56.76)	185 (57.10)	0.97	NS
Secondary infertility (%)	243 (43.24)	139 (42.90)	0.12	NS
Infertility etiology				
Endometrial disorders (%)	56 (9.96)	44 (13.58)		
Ovulatory dysfunction (%)	114 (20.28)	91 (28.09)		
Others (%)	392 (69.75)	189 (58.33)		
Mean endometrial thickness (cm) ±SD	0.90±0.13	0.90±0.13	1.00	NS
Mean no. of embryos transferred ±SD	2.38±0.60	2.36±0.70	0.65	NS
Single embryo transfer (%)	259 (46.09)	180 (55.56)		
Double embryo transfer (%)	303 (53.91)	144 (44.44)		
Mean no. of previous failed transfer cycles ±SD	3.20±0.77	3.20±0.77	1.00	NS
Clinical pregnancy rate (%)	268 (47.69)	105 (32.41)	<0.0001	S
Implantation rate (%)	22.46	14.77	<0.0001	S
Ectopic pregnancy rate (%)	0 (0.00)	2 (0.62)	0.13	
Miscarriage rate (%)	25 (4.45)	21 (6.48)	0.24	
Live birth rate (%)	215 (38.26)	82 (25.31)	0.0001	S
Ongoing pregnancy rate (%)	28 (4.98)	2 (0.62)	0.0003	S

NS: Non-significant, S: statistically significant

Table 2: Demographics and clinical characteristics of ERA non-receptive patients in study versus control groups.

Baseline parameters	EB performed (study group)	EB not performed (control group)	P value	Significance
No. of patients	198	126		
Mean female age (years) ±SD	34.69±4.80	34.88±4.31	0.71	NS
Mean duration of infertility (years) ±SD	8.60±4.06	7.80±4.49	0.10	NS
Primary infertility (%)	114 (57.58)	71 (56.35)		
Secondary infertility (%)	84 (42.42)	55 (43.65)		
Infertility etiology				
Endometrial disorders (%)	27 (13.64)	17 (13.49)		
Ovulatory dysfunction (%)	53 (26.77)	38 (30.16)		
Others (%)	118 (59.60)	71 (56.35)		
Mean endometrial thickness (cm) ±SD	0.90±0.13	0.90±0.14	0.92	NS
Mean no. of embryos transferred ±SD	2.35±0.71	2.36±0.68	0.89	NS
Single embryo transfer (%)	112 (56.57)	68 (55.56)		
Double embryo transfer (%)	86 (43.43)	58 (44.44)		
Mean no. of previous failed transfer cycles ±SD	3.21±0.70	3.19±0.88	0.82	NS

Table 3: Comparison of clinical outcomes in ERA non-receptive patients.

Clinical parameters	EB performed (study group n=198)	EB not performed (control group n=126)	P value	Significance
Clinical pregnancy rate (%)	76 (38.38)	29 (23.02)	0.0058	S
Implantation rate (%)	84/467 (17.99)	29/298 (9.73)	0.0024	S
Ectopic pregnancy rate (%)	1 (0.51)	1 (0.79)	1.0000	NS
Miscarriage rate (%)	13 (6.57)	8 (6.35)	1.0000	NS
Live birth rate (%)	63 (31.82)	19 (15.08)	0.0012	S
Ongoing pregnancy rate (%)	0 (0.00)	2 (1.59)	0.1505	NS

Table 4: Correlation analysis between histologic phases of endometrial biopsy and reproductive outcomes in ERA non-receptive patients.

Clinical parameters	EB proliferative phase (n=61)	EB secretory phase (n=137)	P value	Significance
Clinical pregnancy rate (%)	15 (24.59)	61 (44.53)	0.0122	S
Implantation rate (%)	17/140 (12.14)	67/327 (20.49)	0.0434	S
Ectopic pregnancy rate (%)	1 (1.64)	0 (0.00)	0.3081	NS
Miscarriage rate (%)	7 (11.48)	6 (4.38)	0.1210	NS
Live birth rate (%)	8 (13.11)	55 (40.15)	0.0003	S

DISCUSSION

To our knowledge, this is the first study directly comparing classical histological endometrial dating with ERA-based molecular dating for determining optimal embryo transfer timing in patients with a non-receptive endometrium. Precise identification of the WOI is critical to avoid embryo wastage and reduce the emotional, physical, and financial stress associated with implantation failure. Endometrial non-receptivity has been implicated in approximately one-third to two-thirds of implantation failures, underscoring its central role in reproductive outcomes.[7,8] Our findings demonstrate that embryo transfer performed outside the WOI is associated with significantly reduced pregnancy outcomes, highlighting the importance of precise endometrial timing.

ERA has been proposed as a molecular tool for individualizing embryo transfer timing, with several studies reporting improved outcomes, particularly in RIF.[9] However, its clinical utility remains a subject of ongoing debate as recent evidences has not consistently demonstrated improved live birth rates compared with conventional frozen embryo transfer. Furthermore, its utility appears limited in first embryo transfer cycles or in patients with a favourable prognosis, and it is therefore not recommended as a routine test for unselected populations.[10-12]

In the present study, ERA receptivity was significantly associated with higher clinical pregnancy, implantation, ongoing pregnancy, and live birth rates, reinforcing its association with reproductive success. These findings are consistent with those of Alonso et al, who demonstrated improved IVF outcomes following ERA-guided personalized embryo transfer by aligning embryo transfer with the receptive window.[13]

Interestingly, 36.6% of patients in the ERA-guided personalized embryo transfer (pET) group exhibited a displacement of the WOI, underscoring the frequency of altered implantation timing in this population. This proportion aligns with previous studies conducted by Patel et al, derived from molecular clustering-based assessment of endometrial receptivity.[14] While ERA-guided personalization may improve outcomes in receptive patients, the optimal management of non-receptive cases remains less well defined.

Importantly, histological endometrial phase was also significantly associated with reproductive outcomes. Patients with secretory-phase endometrium demonstrated higher clinical pregnancy, implantation, and live birth rates, along with lower miscarriage rates, compared with those in the proliferative phase. This supports the concept that morphological endometrial maturation reflects functional receptivity and implantation potential. Within the ERA non-receptive cohort, clinical pregnancy rates were comparable between ERA-receptive endometrium and histologically secretory endometrium. This suggests partial concordance between molecular and morphological markers of endometrial maturation. Histological evaluation may therefore provide complementary morphological correlation of endometrial readiness that is not fully captured by transcriptomic profiling. In ERA non-receptive patients, histological dating may assist in refining the characterization of endometrial maturation and implantation window dynamics by identifying delayed or asynchronous secretory transformation. This offers a pragmatic and reproducible adjunct to molecular testing for improving endometrial stratification and optimizing embryo transfer timing. Importantly, the frequent absence of overt histological abnormalities despite molecular non-receptivity suggests a potential dissociation between transcriptomic and structural maturation. This highlights

the complexity of endometrial receptivity and supports the need for integrated assessment approaches.

Limitations

Limitations of this study include its retrospective design, which introduces potential selection bias and limits causal inference. In addition, the potential effect of biopsy-induced endometrial injury ("endometrial scratching") cannot be excluded and may have contributed to improved outcomes, acting as a confounding factor. Prospective randomized controlled trials are required to validate these findings and clarify the independent role of histological dating.

CONCLUSION

In conclusion, this study demonstrates that both ERA-based molecular assessment and histological evaluation are associated with reproductive outcomes in patients with non-receptive endometrium. Histological endometrial maturation shows a strong association with improved implantation and live birth rates and may serve as a complementary tool alongside ERA in selected patients. An integrated diagnostic approach combining molecular and morphological assessment may improve the precision of embryo transfer timing and optimize clinical outcomes. Further prospective studies are warranted to define the clinical utility of this combined strategy.

ACKNOWLEDGEMENTS

Authors would like to thank Ms. Sajjitha Kishore, Ms. Srimathi, Ms. Suguna, and Dr. Stalin for their invaluable support during this study.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Cohen AM, Ye XY, Colgan TJ, Greenblatt EM, Chan C. Comparing endometrial receptivity array to histologic dating of the endometrium in women with a history of implantation failure. Syst Biol Reprod Med. 2020;66(6):347-54.
2. Rubin SC, Abdulkadir M, Lewis J, Harutyunyan A, Hirani R, Grimes CL. Review of Endometrial Receptivity Array: A Personalized Approach to Embryo Transfer and Its Clinical Applications. J Pers Med. 2023;13(5):749.
3. Mei Y, Wang Y, Ke X, Liang X, Lin Y and Wang F. Does endometrial receptivity array improve reproductive outcomes in euploid embryo transfer cycles? a systematic review. Front Endocrinol. 2023;14:1251699.
4. Chae-Kim J, Doyle N, Jahandideh S, O Brien JE, Widra EA, Levy M, et al. Evaluating the endometrial receptivity assay: a nested diagnostic accuracy study within the Synchrony randomized clinical trial. Fertil Steril. 2023;120(6):1255-6.
5. Riestenberg C, Kroener L, Quinn M, Ching K, Ambartsumyan G. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. Fertil Steril. 2021;115:1001-6.
6. Ma J, Gao W, Li D. Recurrent implantation failure: A comprehensive summary from etiology to treatment. Front Endocrinol (Lausanne). 2023;13:1061766.
7. de Ziegler D, Scott RTJr, Pirtea, P. If recurrent implantation failure (RIF) is rare, what could be the cause of repeat unsuccessful ARTs? Fertil Steril 2023;(23):2036-8.
8. Liu Z, Liu X, Wang M, Zhao H, He S, Lai S, et al. The Clinical Efficacy of Personalized Embryo Transfer Guided by the Endometrial Receptivity Array/Analysis on IVF/ICSI Outcomes: A Systematic Review and Meta-Analysis. Front Physiol. 2022;13:841437.
9. Ohara Y, Matsubayashi H, Suzuki Y, Takaya Y, Yamaguchi K, Doshida M, et al. Clinical relevance of a newly developed endometrial receptivity test for patients with recurrent implantation failure in Japan. Reprod Med Biol. 2022;21(1):e12444.
10. Riestenberg C, Kroener L, Quinn M, Ching K, Ambartsumyan G. Routine endometrial receptivity array in first embryo transfer cycles does not improve live birth rate. Fertil Steril. 2021;115(4):1001-6.
11. Glujovsky D, Lattes K, Miguens M, Pesce R, Ciapponi A. Personalized embryo transfer guided by endometrial receptivity analysis: A systematic review with meta-analysis. Hum Reprod. 2023;38(7):1305-17.
12. Xu S, Diao H, Xiong Y, Zhang C, Zhang Y, Zhang Y. The study on the clinical efficacy of endometrial receptivity analysis and influence factors of displaced window of implantation. Sci Rep. 2025;15(1):7326.
13. Alonso MR, Díaz-Gimeno P, Gómez E, Rincón-Bertolín A, Vladimirov Y, Garrido N. Clinical efficiency of embryo transfer performed in receptive vs non-receptive endometrium diagnosed by the endometrial receptivity array (era) test. Fertil Steril. 2014;102(3):pe292.
14. Patel J, Patel A, Banker J, Shah S, Banker M. Personalized embryo transfer helps in improving In vitro fertilization/ICSI outcomes in patients with recurrent implantation failure. J Hum Reprod Sci. 2019;12:59.

Cite this article as: Selvaraj P, Selvaraj K, Sivakumar M, Sudan S, Srinivasan K. Optimizing IVF outcomes in non-receptive endometrium using combined histological dating and ERA: a retrospective study. Int J Reprod Contracept Obstet Gynecol 2026;15:2152-7.