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Unlocking Implantation: A Dual-Compartment Strategy with Hyaluronic Acid and Alpha Lipoic Acid Achieves 88.9% Clinical Pregnancy Rate in Primary Infertility Undergoing IVF/ICSI

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ABSTRACT

Study question: Does a fixed-dose combination of oral hyaluronic acid (HA) and alpha lipoic acid (ALA), administered during IVF/ICSI, improve clinical pregnancy rates in women with primary infertility?

Summary answer: Combined periconceptional supplementation with HA and ALA was associated with a clinical pregnancy rate of 88.9% per embryo transfer, approximately double published global IVF/ICSI benchmarks, with 100% biochemical-to-clinical conversion and no adverse events attributable to either agent.

What is known already: Global IVF/ICSI clinical pregnancy rates remain constrained to 35–45% per transfer cycle. HA is integral to endometrial extracellular matrix remodelling during the implantation window and has been associated with modest improvements in ART outcomes when used as an embryo transfer medium additive. ALA is a mitochondria-targeted amphipathic antioxidant with demonstrated efficacy in reducing reactive oxygen species burden during ovarian stimulation. No prospective clinical study has evaluated their combined use.

Study design, size, duration: Prospective observational case series at a single specialist reproductive medicine centre in Mumbai, India (September–November 2025). Ten women with primary infertility were consecutively enrolled; nine were evaluable after one exclusion for PGT-identified chromosomal embryo anomaly precluding transfer.

Participants/materials, setting, methods: Women aged 22–42 years with confirmed primary infertility scheduled for IVF or ICSI with fresh or frozen embryo transfer. The intervention was a fixed-dose combination tablet containing HA 200 mg and ALA 100 mg, administered orally twice daily (total daily dose: HA 400 mg, ALA 200 mg), initiated concurrent with controlled ovarian stimulation and continued through the luteal phase. The primary outcome was clinical pregnancy rate per embryo transfer, defined as

visualisation of an intrauterine gestational sac on transvaginal ultrasound at 6–7 weeks gestation. Binomial 95% confidence intervals were calculated using the Wilson score method.

Main results and the role of chance: Clinical pregnancy rate was 88.9% (8/9; 95% CI 51.8–99.7%) per embryo transfer. Biochemical pregnancy rate was 88.9% (8/9; 95% CI 51.8–99.7%); biochemical-to-clinical conversion was 100% (8/8; 95% CI 63.1–100%). All eight clinical pregnancies were ongoing at last follow- up. Mean endometrial thickness at transfer was 9.0 mm (SD 0.9; range 7.5–10.0 mm). All nine evaluable participants had triple-line (trilaminar) endometrial morphology. No adverse events attributable to HA or ALA were recorded. The wide confidence intervals reflect the small sample; results are considered hypothesis-generating.

Limitations, reasons for caution: The small evaluable sample (n = 9), single-centre design, and absence of a concurrent randomised control arm preclude causal inference. The independent contributions of HA and ALA cannot be disentangled. The live birth rate was not available due to the short follow-up period. Findings may not generalise to other clinical settings.

Wider implications of the findings: The magnitude, internal consistency, and mechanistic plausibility of these findings provide justification for a well-powered, double-blind, placebo-controlled RCT evaluating the HA and ALA combination in women undergoing IVF/ICSI, with live birth rate as the primary endpoint.

Study funding/competing interests: This study received no external funding. No conflict of interest is declared.

Trial registration number: Not applicable (observational case series).

Keywords: IVF, ICSI, Hyaluronic acid, Alpha lipoic acid, Implantation failure, Endometrial receptivity, Oxidative stress, ART outcomes, Clinical pregnancy rate, Primary infertility, Periconceptional supplementation

INTRODUCTION

Infertility affects an estimated 186 million individuals worldwide, with primary infertility constituting a disproportionate burden in South Asia, where Indian prevalence estimates range from 3.9% to 16.8% of couples of reproductive ages [1]. Assisted reproductive technology (ART), principally IVF and ICSI, is the cornerstone of management for complex infertility; yet global live birth rates per transfer cycle remain constrained to 30–40%, with implantation failure and suboptimal endometrial receptivity accounting for the majority of cycle failures [2].

Implantation is a precisely orchestrated molecular dialogue between a developmentally competent embryo and a receptive endometrium. The implantation window (approximately days 20–24 of a natural cycle) is characterised by transformation of the endometrial surface and extracellular matrix (ECM) that enables trophoblast attachment, invasion, and decidualisation. Disruption of any element of this process, whether from oxidative stress, impaired ECM remodelling, or suboptimal endometrial vascularity, results in implantation failure. In the IVF/ICSI context, controlled ovarian hyperstimulation further alters endometrial receptivity through supraphysiological oestrogen exposure, making periconceptional interventions that stabilise and enhance the endometrial environment of particular clinical relevance.

Hyaluronic acid (HA) is a high-molecular-weight, non-sulphated glycosaminoglycan and a principal structural component of the endometrial ECM. During the implantation window, HA accumulates preferentially at the endometrial luminal epithelium, where it mediates trophoblast–epithelial adhesion through CD44 and RHAMM receptor binding, facilitates fibronectin and laminin scaffold organisation critical

for trophoblast invasion, and regulates endometrial fluid viscosity. HA also acts as an endogenous anti-inflammatory agent by competing with lipopolysaccharide for CD44 receptor binding, thereby modulating endometrial macrophage activation. In clinical embryology, HA-enriched embryo transfer media have been associated with modest but statistically significant improvements in implantation and live birth rates [3,4]. However, the effect of oral HA supplementation on IVF/ICSI outcomes has not been rigorously characterised.

Alpha lipoic acid (ALA), a naturally occurring dithiol compound synthesised in mitochondria, is unique among antioxidants in its amphipathic solubility, enabling access to both hydrophilic and lipophilic cellular compartments, and its capacity to regenerate endogenous antioxidants including glutathione, vitamins C and E, and coenzyme Q10 [5]. In the context of ART, oxidative stress represents a central pathophysiological mechanism: Reactive oxygen species (ROS) generated during ovarian stimulation impair oocyte mitochondrial membrane integrity, disrupt the spindle apparatus, promote DNA strand breaks, and compromise early embryo morphokinetics [6,7]. ALA's dual antioxidant and mitochondria-regenerating properties position it as a mechanistically precise agent for oocyte and embryo quality preservation. Furthermore, ALA activates the Nrf2–Keap1 antioxidant response pathway, inducing endogenous cytoprotective gene expression in granulosa cells and the endometrium, and exerts anti-inflammatory effects via NF-κB inhibition [8].

Despite their complementary and non-overlapping mechanisms—with HA acting principally on the endometrial receptive milieu and ALA acting principally on the oocyte/embryo oxidative environment—no prospective clinical study has examined their combined use in women undergoing IVF/ICSI. The present prospective observational case series was designed to address this gap, characterising implantation outcomes, endometrial parameters, and safety in a real-world clinical cohort at a specialist reproductive medicine centre in Mumbai, India.

MATERIALS AND METHODS

Study Design and Ethics

This prospective, single-centre, observational case series was conducted at Spandan Test Tube Baby and Advanced Reproductive Centre, Andheri, Mumbai, India, between 24 September and 15 November 2025. The study was conducted in full accordance with the ethical principles of the Declaration of Helsinki (revised 2013) and Indian Council of Medical Research (ICMR) guidelines for biomedical and health research involving human participants. Institutional ethical committee approval was obtained before enrolment. Written informed consent was obtained from all participants. All patient identifiers have been replaced with anonymised codes (P1–P10) throughout.

Eligibility Criteria

Inclusion criteria were: (i) married women with confirmed primary infertility (inability to conceive after 12 months or more of unprotected intercourse, or 6 months or more in women aged 35 years or older); (ii) age 22–42 years; (iii) scheduled for IVF or ICSI with fresh or frozen embryo transfer at the study centre; and (iv) willingness to initiate and maintain HA and ALA supplementation from enrolment through embryo transfer and the early luteal phase. The exclusion criterion was chromosomal embryo anomaly identified on preimplantation genetic testing (PGT) precluding embryo transfer (applied to P7, who was excluded from efficacy analysis).

Intervention

The combination tablet was initiated on the day of enrolment, concurrent with commencement of controlled ovarian stimulation. Each tablet contained HA 200 mg and ALA 100 mg as a fixed-dose combination,

administered orally twice daily with food, delivering a total daily dose of HA 400 mg and ALA 200 mg. The twice-daily dosing schedule was chosen to maintain consistent systemic and endometrial exposure throughout the day, consistent with the pharmacokinetic profiles of both agents. The combination tablet was continued through the luteal support phase until serum beta-hCG assessment at 14 days post-transfer. Compliance was monitored via structured daily patient diaries reviewed at each scheduled clinical visit (**Table 1**).

Table 1: Proposed mechanisms of action of HA and ALA relevant to IVF/ICSI implantation

Agent	Primary Target	Mechanism of Action	Relevant Pathway	Expected ART Benefit
Hyaluronic Acid (HA)	Endometrial ECM and luminal epithelium	CD44/RHAMM-mediated trophoblast adhesion; ECM scaffolding; anti-inflammatory via CD44–LPS competition	Endometrial receptivity window	Enhanced embryo attachment; improved endometrial thickness and morphology
Alpha Lipoic Acid (ALA)	Oocyte/embryo mitochondria	ROS scavenging (amphipathic); Nrf2–Keap1 activation; GSH/CoQ10/vitamins C and E regeneration; NF-κB inhibition	Mitochondrial redox balance; antioxidant cascade	Preserved oocyte quality; improved embryo morphokinetics; reduced DNA strand breaks
HA + ALA Combined	Endometrium and oocyte/embryo	Complementary dual-compartment protection: receptive endometrium and competent embryo	Implantation cascade	Synergistic improvement in clinical pregnancy rate

ECM = extracellular matrix; ROS = reactive oxygen species; GSH = glutathione; CoQ10 = coenzyme Q10; LPS = lipopolysaccharide; Nrf2 = nuclear factor erythroid 2-related factor 2; NF-κB = nuclear factor kappa-light-chain-enhancer of activated B cells.

IVF/ICSI Protocol and Embryo Transfer

Controlled ovarian stimulation, oocyte retrieval, fertilisation (IVF or ICSI as clinically indicated), embryo culture, and transfer were performed according to standard departmental protocols under the direction of the principal investigator (V.S.). Fresh embryo transfer was performed in eight of nine evaluable participants; one participant (P6) underwent a programmed frozen embryo transfer (FET) cycle. Endometrial thickness and morphology (triple-line versus non-triple-line pattern) were assessed by standardised transvaginal ultrasonography on the day of embryo transfer. Embryo quality was graded by the senior embryologist (Gardner criteria for blastocysts; Istanbul consensus for cleavage-stage embryos). Standard luteal support with progesterone was administered to all participants.

Outcome Measures

The primary outcome was clinical pregnancy rate per embryo transfer, defined as visualisation of an intrauterine gestational sac (with or without yolk sac) on transvaginal ultrasound at 6–7 weeks gestation.

Secondary outcomes were: (i) biochemical pregnancy rate (serum beta-hCG >5 IU/L at 14 days post-transfer); (ii) biochemical-to-clinical conversion rate; (iii) ongoing pregnancy rate (fetal cardiac activity on ultrasound); (iv) mean endometrial thickness at transfer; (v) endometrial morphology; and (vi) adverse events attributable to HA or ALA.

Statistical Analysis

Descriptive statistics are presented as mean ± SD for continuous variables and as frequencies with proportions for categorical variables. Binomial 95% confidence intervals (CIs) for proportions were calculated using the Wilson score method. Given the exploratory nature and small sample size, no inferential hypothesis testing was performed; data are presented as hypothesis-generating. All calculations were performed in Microsoft Excel (version 2021).

RESULTS

Participant Characteristics

Ten women were consecutively enrolled; one (P7, age 38, unexplained infertility, PCOS) was excluded from efficacy analysis due to PGT-identified chromosomal embryo anomalies precluding transfer. Nine evaluable participants had a mean age of 33.0 years (SD 6.2; range 22–42 years) and a mean BMI of 22.8 kg/m² (SD 2.4; range 20.0–27.6 kg/m²). Mean duration of primary infertility was 7.4 years (SD 2.7; range 5–13 years). Infertility aetiologies were: female-factor (n = 4; 44.4%), unexplained (n = 3; 33.3%), combined male and female factor (n = 1; 11.1%), and male-factor (n = 1; 11.1%). Four participants (44.4%) had significant comorbidities: diabetes mellitus (n = 2) and thyroid disorder (n = 3; one participant had both). Full baseline and cycle characteristics are provided in (**Table 2**).

Table 2: Baseline patient demographics, infertility profile, and IVF/ICSI cycle parameters

Patient	Age (yr)	BMI	Duration	Aetiology	Comorbidities	Cycle	ET (mm)	Embryos Tx	Outcome
P1	31	21.0	9 yr	Female factor	None	Fresh	8.0	2	Positive/Clinical
P2	34	21.0	9 yr	Female factor	None	Fresh	7.5	1	Positive/Clinical
P3	35	27.6	9 yr	Male + Female	Diabetes	Fresh	10.0	2	Positive/Clinical
P4	25	22.0	6 yr	Male factor	None	Fresh	9.0	2	Positive/Clinical
P5	37	24.0	9 yr	Female factor	Diabetes; Thyroid	Fresh	8.0	2	Positive/Clinical
P6	22	20.0	5 yr	Female	Thyroid	Frozen	10.0	2	Positive/Clinical

Patient	Age (yr)	BMI	Duration	Aetiology	Comorbidities	Cycle	ET (mm)	Embryos Tx	Outcome
				factor		ET			
P7*	38	29.0	3 yr	Unexplained	PCOS	PGT	10.0	N/A	Excluded (PGT)
P8	32	24.0	13 yr	Unexplained	Diabetes	Fresh	9.0	2	Positive/Clinical
P9	42	24.0	5 yr	Combined	None	Fresh	8.0	1	Negative (Failed)
P10	37	20.0	5 yr	Unexplained	Thyroid	Fresh	10.0	2	Positive/Clinical

*P7 excluded: chromosomal embryo anomaly on PGT; transfer not performed. ET = endometrial thickness at transfer (mm); Tx = transferred; FET = frozen embryo transfer; PGT = preimplantation genetic testing.

Compliance and Tolerability

All nine evaluable participants initiated the fixed-dose combination tablet and maintained 100% compliance across all diary records throughout the study period. No participant reported any adverse event plausibly related to either agent. Specifically, no gastrointestinal intolerance, dermatological reactions, or hypoglycaemic episodes were recorded. The two participants with diabetes mellitus (P3, P8) tolerated the full twice-daily regimen without glycaemic disturbance, consistent with published tolerability data for oral ALA at doses of 200 mg/day or less.

Endometrial Parameters

Mean endometrial thickness at embryo transfer was 9.0 mm (SD 0.9; range 7.5–10.0 mm). All successful implantations (n = 8) occurred in participants with endometrial thickness of 7.5 mm or greater and triple-line (trilaminar) morphology on ultrasound. The participant with failed implantation (P9) also had adequate endometrial thickness (8.0 mm) and trilaminar morphology, confirming that endometrial thickness alone was not the differentiating factor in the single failure, which was attributable instead to fair embryo quality, advanced maternal age (42 years), and combined-factor infertility.

Pregnancy Outcomes

Among nine evaluable participants, eight achieved a positive serum beta-hCG at 14 days post-transfer (biochemical pregnancy rate: 88.9%; 95% CI 51.8–99.7%). All eight biochemically positive participants had an intrauterine gestational sac confirmed on transvaginal ultrasound at 6–7 weeks gestation (clinical pregnancy rate: 88.9% per transfer; 95% CI 51.8–99.7%; biochemical-to-clinical conversion: 100%; 95% CI 63.1–100%). All eight clinical pregnancies were ongoing at the time of last recorded follow-up. The sole implantation failure occurred in P9 (age 42, combined infertility, fair-quality single embryo transferred), consistent with the well-characterised influence of advanced maternal age and embryo morphological grade on implantation probability independent of supplementation effects (Table 3, 4).

Table 3: Individual HA and ALA efficacy: endometrial response, biochemical, and clinical pregnancy outcomes

Patient	Age	Combination Tablet	Dosing	Compliance	ET (mm)	beta-hCG (IU/L)	Clinical Pregnancy	Status at Follow-up
P1	31	HA 200 mg + ALA 100 mg	Twice daily	100%	8.0	100	Confirmed	Ongoing
P2	34	HA 200 mg + ALA 100 mg	Twice daily	100%	7.5	220	Confirmed	Ongoing
P3	35	HA 200 mg + ALA 100 mg	Twice daily	100%	10.0	400	Confirmed	Ongoing
P4	25	HA 200 mg + ALA 100 mg	Twice daily	100%	9.0	500	Confirmed	Ongoing
P5	37	HA 200 mg + ALA 100 mg	Twice daily	100%	8.0	105	Confirmed	Ongoing
P6	22	HA 200 mg + ALA 100 mg	Twice daily	100%	10.0	500	Confirmed	Ongoing
P8	32	HA 200 mg + ALA 100 mg	Twice daily	100%	9.0	150	Confirmed	Ongoing
P9	42	HA 200 mg + ALA 100 mg	Twice daily	100%	8.0	<0.1	Not confirmed	Failed implantation
P10	37	HA 200 mg + ALA 100 mg	Twice daily	100%	10.0	125	Confirmed	Ongoing

ET = endometrial thickness (mm) at day of embryo transfer. Beta-hCG assessed at 14 days post-transfer. Clinical pregnancy defined as intrauterine gestational sac on ultrasound at 6–7 weeks gestation. HA = hyaluronic acid; ALA = alpha lipoic acid.

Table 4: Summary efficacy and safety outcomes

Outcome Measure	Result	95% CI / Range
Biochemical pregnancy rate (beta-hCG positive at 14 days post-transfer)	**8/9 (88.9%)**	95% CI 51.8–99.7%
Clinical pregnancy rate (intrauterine gestational sac at 6–7 weeks)	**8/9 (88.9%)**	95% CI 51.8–99.7%
Biochemical-to-clinical pregnancy conversion	**8/8 (100%)**	95% CI 63.1–100%
Ongoing pregnancy rate at last follow-up	**8/9 (88.9%)**	95% CI 51.8–99.7%
Mean endometrial thickness at transfer	9.0 mm (SD 0.9 mm)	Range 7.5–10.0 mm
Triple-line endometrial morphology (% evaluable)	9/9 (100%)	N/A
Compliance (HA and ALA)	9/9 (100%)	N/A
Adverse events attributable to HA or ALA	0/9 (0%)	N/A
Published global IVF/ICSI CPR benchmark (comparator)	~35–45%	Kupka 2016; CDC 2021

CI = confidence interval (Wilson score method). Published benchmark represents aggregate European and US registry data for fresh and frozen IVF/ICSI cycles (Kupka et al., 2016; CDC, 2021). CPR = clinical pregnancy rate.

DISCUSSION

This prospective observational case series reports a clinical pregnancy rate of 88.9% (8/9; 95% CI 51.8– 99.7%) per embryo transfer in women with primary infertility receiving combined oral HA and ALA supplementation during IVF/ICSI, a figure substantially exceeding published global registry benchmarks of 35–45% [9,10]. While the absence of a concurrent randomised control arm precludes causal attribution, the magnitude, internal consistency, and mechanistic plausibility of these findings constitute a compelling hypothesis requiring investigation in an appropriately powered randomised controlled trial.

Hyaluronic Acid: Endometrial Mechanisms and Clinical Evidence

The endometrial effects of HA are mediated principally through two surface receptors. CD44, constitutively expressed on endometrial stromal and epithelial cells, binds HA to initiate cytoskeletal rearrangement and focal adhesion kinase (FAK) signalling, promoting stromal cell migration and decidualisation. RHAMM (receptor for HA-mediated motility), transiently upregulated during the implantation window, facilitates trophoblast motility and invasion. In this cohort, the uniformly trilaminar endometrial morphology (100% of evaluable participants) and mean endometrial thickness of 9.0 mm, both associated with maximal

implantation probability, are consistent with HA-mediated augmentation of the endometrial ECM. The use of HA-enriched transfer media in clinical IVF has been demonstrated in a Cochrane review to increase live birth rates by approximately 8% over standard media (OR 1.40, 95% CI 1.22–1.61) [3]; the present data raise the hypothesis that systemic oral HA supplementation may extend and amplify this benefit beyond the point of transfer to include the broader peri-implantation endometrial environment.

Alpha Lipoic Acid: Oocyte and Embryo Protective Mechanisms

The oocyte is acutely vulnerable to oxidative damage during controlled ovarian stimulation. ROS generated during folliculogenesis impair mitochondrial membrane potential, disrupt the cytoskeletal spindle apparatus during meiosis I and II, and induce DNA adducts in oocyte mtDNA, collectively increasing aneuploidy rates and reducing embryo developmental competence [6,7]. ALA, as an amphipathic dithiol, penetrates the inner mitochondrial membrane where it scavenges superoxide, hydrogen peroxide, and hydroxyl radicals directly, and in its reduced form (dihydrolipoic acid; DHLA) regenerates the endogenous glutathione peroxidase cycle [5]. In this cohort, eight of nine evaluable participants produced good-quality embryos. The single fair-quality embryo (P9, age 42) was attributable to irreversible age-related mitochondrial depletion, a process that ALA supplementation at the doses employed cannot fully overcome. Among the eight participants with good- quality embryos, all demonstrated successful clinical pregnancy, representing 100% implantation efficacy within this subgroup, suggesting meaningful ALA-mediated oocyte protection in a population where comorbidities would otherwise confer elevated oxidative stress.

Synergistic Rationale for the HA and ALA Combination

The mechanistic case for HA and ALA as a combination rests on their non-overlapping and potentially synergistic targets. HA operates at the endometrial compartment, preparing the receptive surface for embryo adhesion and trophoblast invasion, while ALA operates at the gamete and embryo compartment, preserving intrinsic developmental competence. In conventional IVF practice, clinical attention is frequently directed at either endometrial preparation or embryo selection in isolation; the present data suggest a dual-compartment strategy may offer additive benefit. Furthermore, ALA's NF-κB inhibitory activity reduces pro-inflammatory cytokine expression (IL-1β, TNF-α) at the endometrial surface which, when excessive, is associated with implantation failure through impairment of trophoblast invasion—providing a second pathway through which ALA may complement HA's receptivity-enhancing effects.

Clinical Contextualisation

This cohort was intentionally heterogeneous in infertility aetiology and comorbidity profile. Particularly noteworthy are the successful clinical pregnancies achieved in P5 (age 37, diabetes mellitus and hypothyroidism, 9-year infertility duration) and P8 (age 32, unexplained infertility of 13-year duration, diabetes mellitus), two participants in whom systemic oxidative stress associated with diabetes and insulin resistance would be expected to compromise oocyte quality and endometrial function. The high beta-hCG values in P3 (400 IU/L) and P4 (500 IU/L) at 14 days post-transfer suggests robust trophoblastic proliferation, consistent with competent embryo implantation and invasion. These observations align with experimental data demonstrating ALA-mediated protection of granulosa cell function in hyperglycaemic conditions and HA-mediated attenuation of inflammatory endometrial signalling in insulin-resistant states.

Limitations

The following limitations require explicit declaration. The small evaluable sample (n = 9) limits statistical power and precludes multivariate adjustment for confounders. The single-centre design and absence of a concurrent randomised control group prevent causal inference; observed outcomes may partially reflect centre-level expertise, patient selection, and the Hawthorne effect of intensive clinical monitoring. Both HA

and ALA were co-administered throughout the study; their independent effects cannot be disentangled from this dataset, a limitation that a future factorial RCT design could address. Supplementation doses were fixed across participants without pharmacokinetic or biomarker-guided individualisation. The live birth rate, which is the gold-standard ART outcome, cannot be reported due to the short follow-up period. Finally, findings from a Mumbai tertiary centre may not be generalisable to other healthcare settings.

CONCLUSION

This prospective case series demonstrates that oral combined hyaluronic acid (400 mg/day) and alpha lipoic acid (200 mg/day), administered from the onset of controlled ovarian stimulation through the luteal phase, was associated with a clinical pregnancy rate of 88.9% per embryo transfer in nine evaluable women undergoing IVF/ICSI, with 100% biochemical-to-clinical pregnancy conversion and no attributable adverse events. By concurrently targeting endometrial receptivity through HA-mediated CD44/RHAMM signalling and embryo competence through ALA-mediated mitochondrial antioxidant protection, this combination addresses the two principal determinants of implantation failure within a single, well-tolerated oral regimen. These findings provide a clinically and mechanistically grounded basis for a randomised controlled trial evaluating HA and ALA supplementation specifically in women with recurrent implantation failure, with live birth rate as the primary endpoint.

Authors' roles

V.S.: Study design, clinical conduct, embryo transfer procedures, data acquisition. T.B.: Conceptualisation, protocol development, data analysis, manuscript drafting and critical revision. Both authors approved the final manuscript and are accountable for all aspects of the work.

DECLARATIONS

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Conflict of interest: The authors declare no financial or non-financial conflicts of interest in relation to this study.

Ethical approval: Conducted in accordance with the Declaration of Helsinki (revised 2013) and ICMR guidelines. Institutional ethical committee approval obtained prior to enrolment. Written informed consent obtained from all participants.

Data availability: Anonymised participant-level datasets are available from the corresponding author upon reasonable request, subject to institutional data governance and participant consent provisions.

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