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Original Article

Ovarian Tissue Transplantation Using Autologous Platelet-Rich Plasma: A Pilot Clinical Trial

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ABSTRACT **Objective:** To study the feasibility and safety of using autologous platelet-rich plasma (PRP) during laparoscopic orthotopic reimplantation of cryopreserved ovarian tissue.

Design: Single-center, interventional, pilot, prospective, cohort study.

Setting: Tertiary university hospital (IRCCS-Azienda Ospedaliero-Universitaria di Bologna-Policlinico Sant'Orsola).

Participants: Five eligible consecutive patients, who previously cryopreserved ovarian tissue before chemo(radio) therapy for oncologic diseases and were scheduled for orthotopic reimplantation with the use of autologous PRP to treat iatrogenic premature ovarian failure, were compared with a historical cohort of 19 similar patients who underwent orthotopic reimplantation without the use of autologous PRP.

Interventions: Before surgery, autologous PRP (10 mL) was transformed into gel using calcium gluconate. Autotransplantation was performed by standard four-port laparoscopy, creating pockets in the ovarian cortex and/or peritoneal cavity to insert frozen-thawed ovarian tissue fragments covered by gelled PRP. Pre-, intra-, and postoperative data were collected (characteristics of the study population, adverse reactions, operative time, surgical complications, menstrual resumption).

Results: Study outcomes included: rate of adverse reactions, rate of intra- and postoperative surgical complication, total intraoperative time, rate of restored endocrine function, and median (absolute range) time to first menses (expressed in months) during follow-up. The mean (range) age at ovarian tissue retrieval and at transplantation were 30 (27−31) and 38 (36−41) years for the PRP group, and 33 (24−34) and 41 (34−42) years for the non-PRP group. During the study period, no intra- and postoperative complication nor adverse reaction to PRP use was observed. All patients treated with PRP experienced resumption of regular ovarian function after a median (range) period of 3 (1−6) months, with a significant shorter time in the PRP group. One patient in the experimental group conceived 3 months after surgery and had one live birth at the time of this report.

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Trial Registration Number: NCT06261658

IRB Approval and Informed Consent: The study received ethical approval by the Institutional Review Board of IRCCS Azienda Ospedaliero-Universitaria di Bologna (Approval No.: 363/2022/Sper/AOUBo) and complied with the ethical principles outlined in the Declaration of Helsinki. All participants provided written informed consent for inclusion and for use of anonymized data.

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Conclusion: Autologous PRP appears to be a feasible and safe adjunct in orthotopic ovarian tissue transplantation, potentially enhancing the restoration of ovarian function. Journal of Minimally Invasive Gynecology (2026) 33, 963−970.

Keywords: Fertility preservation; Minimally invasive surgery; Ovarian tissue biopsy; Oncofertility; Transplant

Advancements in cancer treatment have significantly improved survival rates among patients, shifting increasing attention toward quality of life after recovery. Among the long-term side effects of chemotherapy and radiotherapy, one of the most critical for young female survivors is the irreversible damage to ovarian reserve, often resulting in premature ovarian insufficiency (POI) and infertility [1]. This issue has led to a growing interest in fertility preservation strategies, particularly after the dramatic increase of oncological cases among fertility-age women [2,3].

In this context, cryopreservation of ovarian tissue prior to gonadotoxic treatments followed by autologous orthotopic transplantation presents one of the most promising fertility preservation options. Several studies have demonstrated that this technique can restore ovarian function and fertility, resulting in spontaneous pregnancies and live births [4]. However, a major limitation of this approach is the substantial loss of follicles occurring shortly after reimplantation, which significantly reduces graft efficiency and longevity. Follicular depletion is primarily attributed to ischemia-reperfusion injury during the early post-transplantation period, but additional mechanisms, including oxidative stress, inflammatory responses, stromal damage, and apoptosis induced by the freeze-thaw process, have also been implicated.

Platelet-rich plasma (PRP) is an autologous blood-derived product obtained through centrifugation that concentrates platelets and induces their activation, leading to a release of a wide array of bioactive molecules, including growth factors, cytokines, and chemokines. These factors are known to angiogenesis, modulate inflammation, and support tissue repairs and regeneration [5,6]. In reproductive medicine, clinical and experimental evidence suggests that PRP may enhance folliculogenesis and improve ovarian function, although data remain heterogeneous and mechanisms incompletely understood [7,8].

Based on these properties, PRP could represent a potential adjuvant to improve ovarian graft revascularization and reduce ischemic follicular loss following ovarian tissue transplantation (OTT).

Nevertheless, despite its favorable safety profile in other medical fields, clinical data regarding the use of PRP during OTT are currently lacking.

We hypothesized that the addition of autologous PRP to cryopreserved ovarian tissue during orthotopic transplantation would be safe and could promote earlier functional recovery of the graft. Therefore, this pilot clinical study aimed to evaluate the safety of PRP use during OTT and to provide preliminary data on early effectiveness in terms of menstrual resumption (Supplemental Fig. 1).

Materials and Methods

Study Protocol and Selection Criteria

This is a single-center, interventional, prospective, cohort, pilot study carried out at the Gynecology and Human Reproductive Pathophysiology Unit, IRCCS-University Hospital of Bologna, Italy. The study was conducted according to a protocol *a priori* defined and registered on ClinicalTrials.gov (ID: NCT06261658; release date: February 15, 2024). The study was reported in accordance with the CONSORT extension to pilot and feasibility trials [9].

We enrolled all consecutive patients with a diagnosis of POI who had previously cryopreserved their ovarian tissue at the Cryobank of the Gynecology and Human Reproduction Physiopathology Unit, IRCCS-Azienda Ospedaliero-Universitaria di Bologna, and were scheduled for laparoscopic autologous orthotopic OTT from March 1, 2024, to December 29, 2024. Inclusion criteria included negative serological screening for HIV, HBV, HCV, and Treponema pallidum; negative cervical cytology; oncological clearance for undergoing transplantation; signed written informed consent. Exclusion criteria included: histological or molecular evidence of malignant contamination in cryopreserved ovarian tissue; endometriosis; uncontrolled or untreated endocrine disorders (i.e., uncompensated thyroid dysfunction, type 1 or type 2 diabetes); body mass index ≥30 kg/m^2; circulating platelet level <150 000/mm^3; active bacterial infection, ongoing use of anticoagulants; and hemorrhagic diathesis. All exclusion criteria were applied to minimize potential confounding factors that could independently affect graft survival, revascularization, endocrine recovery, or the safety profile of the procedure and of adjuvant PRP use.

Subsequently, the study cohort was compared to a control group consisting of patients who had previously undergone standard laparoscopic autologous orthotopic OTT without PRP at the same institution [10].

Study Outcomes

The primary study outcome was the safety of cryopreserved OTT combined with autologous PRP in terms of rate of adverse reactions, median total operative time, and rate of surgical complications.

The secondary outcome was the early effectiveness of cryopreserved OTT combined with autologous PRP,

evaluated as the rate and median time of menstrual resumption at 6 months after transplantation.

Specifically:

- adverse reactions, graded using the Common Terminology Criteria for Adverse Events [11];
- total operative time was calculated from skin incision to skin closure, including the simultaneous preparation of gelled PRP;
- surgical complications were classified as intraoperative (unexpected events during surgery) or postoperative (occurring within 30 days, e.g., infections or bleeding) and graded according to the Clavien−Dindo classification [12];
- menstrual resumption was monitored through monthly telephone interviews. Menstrual resumption was defined as spontaneous menstrual cycles occurring every 21 to 34 days for at least three consecutive months.

Patients' Management and Data Collection

Ovarian Tissue Cryopreservation

Ovarian tissue was harvested according to Paradisi et al [13] protocol. Immediately after retrieval, samples were transferred into sterile maintaining solution. In the laboratory, trained biologists processed the ovarian cortex into fragments of approximately 1 cm × 2 mm × 1 mm and cryopreserved them using a slow-freezing protocol according to Fabbri et al [14].

Analysis of Fresh and Thawed Ovarian Tissue

Histological assessments were conducted both at the time of harvesting (fresh tissue) and after rapid thawing (cryopreserved tissue). These analyses included assessment of follicular developmental stages according to Gougeon [15], follicular density (number of follicles/mm^2), and morphology of follicles and stromal cells. To exclude malignancy, immunohistochemistry and molecular testing were performed [16−18]. Specifically, ovarian tissue was screened: by immunohistochemistry for CD30-positive cells from patients with Hodgkin lymphoma; by real-time polymerase chain reaction (RT-PCR) for the EWS−FLI1 fusion transcript from patients with Ewing sarcoma; by immunohistochemistry for pan-cytokeratin (MNF116) and by quantitative RT-PCR for breast-specific markers (GCDFP-15, MGB1, and SBEM) from patients with breast cancer. One tissue fragment (∼2 mm × 2 mm × 1 mm) from each ovary was fixed in 4% formaldehyde, paraffin-embedded, and sectioned (4 μm). Hematoxylin and eosin staining was applied to alternate serial sections, while immunohistochemistry was performed on the remaining slides to detect micrometastases. In addition, molecular testing through RT-PCR was performed according to Fabbri et al [10,17].

Autologous PRP Preparation

PRP was prepared at the Regenerative Medicine Unit of the Immunohematology and Transfusion Medicine Service (SIMT-AMBO), Rizzoli Orthopedic Institute, Bologna. PRP collection was performed only after completion of chemotherapy and following oncological clearance, with no evidence of active disease, and a few days prior to ovarian tissue reimplantation.

After confirming eligibility, 300 mL of peripheral blood was collected. Anticoagulant (ACDA) was added at a 1:10 ratio. Samples were first centrifuged at 1800 RPM for 10 minutes at 20°C, separating platelet-poor plasma, the buffy coat, and red blood cells. A second centrifugation (3500 RPM for 10 minutes at 20°C) concentrated the PRP, yielding approximately 10 mL with ∼1000 000 PLT/mL (±20%). The PRP was aliquoted into 5 mL mini-bags using a closed system (PRPS10 Kit) and frozen at −30°C.

OTT with Autologous PRP

Patients with POI and oncological/hematological clearance expressing a desire to regain fertility were counseled regarding the possibility of autologous OTT. Extensive medical evaluation was performed to determine suitability for the procedure. Procedures were performed by an experienced surgical team.

All ovarian tissues were cryopreserved with the slow freezing method and thawed with the rapid thaw approach, as we previously reported [13].

For patients who underwent OTT with autologous PRP, ovarian tissue was thawed and transferred to the operating theatre in PRP-containing medium at room temperature. The thawed ovarian samples were first bathed in liquid PRP and subsequently embedded in PRP activated with calcium gluconate to induce platelet gel formation (Supplemental Fig. 2).

Under general anesthesia, laparoscopy was performed using a four-port approach. Given the lack of standardized guidelines on the optimal amount of tissue to thaw for transplantation, and the limited reliability of precryopreservation ovarian reserve assessment after chemotherapy, the volume of tissue transplanted was guided by follicle density and patient preferences.

Ovarian fragments suspended in platelet gel were inserted into ovarian and subperitoneal pockets at the level of the ovarian fossa [16]. The distribution of ovarian fragments amount in the graft sites was based on pelvic anatomy (e.g., residual ovarian volume, presence of previous adhesions) and prior treatment history. Graft sites were closed using 4-0 Vicryl sutures (Supplemental Fig. 3A, B).

Statistical Analysis

Categorical variables were presented as counts and percentages, and their comparisons between groups were performed using Fisher's exact test. Continuous variables were expressed as median [interquartile range], and their differences between the two groups were analyzed using the Mann−Whitney *U* test.

Statistical matching and covariate adjustment (multivariable analysis) were not applied for two main reasons: the limited sample size and the absence of relevant differences between the two study groups in baseline and intraoperative characteristics. Time to menstrual resumption was analyzed using Kaplan−Meier survival curves. Differences between survival distributions were tested using the Peto−Peto−Prentice test, which accommodates nonproportional hazards [19,20].

The significance level was set at $p \leq \cdot 05$, and all tests were two-sided. All analyses were performed using Stata18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC).

Results

Study Population

During the study period, 7 patients required laparoscopic autologous orthotopic OTT. Two (29%) patients were excluded from the study since they did not meet the selection criteria: 1 patient (14%) did not sign informed consent, and 1 (14%) patient showed circulating platelet level <150 000/mm^3 at the preoperative blood exams testing. As a result, a total of 5 (71%) patients were enrolled in the study.

The control group used for comparisons consisted of 19 patients and previously undergone standard laparoscopic autologous orthotopic OTT at the same institution [10].

Table 1 summarizes the hormonal treatments received by patients in the study group prior to OTT. Table 2 shows a comparison of the intraoperative and demographic characteristics of the study and control groups without finding any significant difference.

Table 1

Gonadotoxic and adjuvant hormonal treatments received by patients in the study cohort prior to ovarian tissue transplantation.

Patient	1	2	3	4	5
Disease	Hodgkin lymphoma	Ewing sarcoma	Breast cancer	Breast cancer	Breast cancer
Chemotherapy before OTC	No	No	No	No	No
Anti-neoplastic treatment after OTC	Adriamycin, bleomycin, vinblastine, dacarbazine	Vincristine, doxorubicin, ifosfamide + Ifosfamide, vincristine + Ifosfamide, etoposide	Epirubicin, cyclophosphamide + Taxol + trastuzumab	Adriamycin, cyclophosphamide + Taxol	5-fluorouracil, epidoxorubicin, cyclophosphamide + Taxol
Hormonal therapy after OTC	GnRH analog for 1 yr, estrogen-progestin	No	GnRH analog	GnRH analog	GnRH analog

GnRH = gonadotropin-releasing hormone; OTC = ovarian tissue cryopreservation.

Table 2

Comparison of demographic and intraoperative characteristics between the study cohort (PRP group) and the previous controls (non-PRP group) undergoing ovarian tissue transplantation.

Data	PRP (*N* = 5)	No-PRP (*N* = 19)	p-Value
Age at OTC (yr)	30 [27−31]	33 [24−34]	.268
Age at OTT (yr)	38 [36−41]	41 [34−42]	.688
BMI (kg/m^2)	25 [19−27]	22 [19−24]	.278
Caucasian ethnicity	5 (100)	19 (100)	\
Smoke	2 (40.0)	1 (5.3)	.099
Chemotherapy before OTC	0	0	\
Number of fragments transplanted	12 [11−12]	10 [5−15]	.614
Number of fragments transplanted in ovary pockets	6 (6−6)	5 (3−6)	.350
Number of fragments transplanted in subperitoneal pockets	6 (5−6)	2 (0−6)	.208

BMI = body mass index; OTC = ovarian tissue cryopreservation; OTT = ovarian tissue transplantation.
Values are reported as *n* (%) or median [interquartile range].

Table 3

Postoperative outcomes and rate of menstrual resumption in the study cohort (PRP group) compared with the previous controls (non-PRP group) after ovarian tissue transplantation.

Outcomes	PRP ($N = 5$)	No-PRP ($N = 19$)	p-Value
Adverse reactions	0 (0.0)	0 (0.0)	\
Total operative time (min)	76 [75−100]	100 [75−110]	.202
Perioperative complications*	0 (0.0)	0 (0.0)	\
Rate of menstrual resumption within 6 mo	5 (100.0)	14 (73.7)	.274

OTC = ovarian tissue cryopreservation; OTT = ovarian tissue transplantation.
Values are reported as *n* (%) or median [interquartile range].
* Includes intraoperative (unexpected events during surgery) or postoperative (occurring within 30 days, e.g., infections or bleeding) complications.

Study Outcomes

About the safety of cryopreserved OTT combined with autologous PRP, no adverse reaction related to the intraoperative use of autologous PRP was reported, median total operative time was 76 minutes, and no surgical complication was reported. No significant difference was found compared with controls (Table 3).

About the early effectiveness, menstrual resumption, defined as spontaneous first menstrual bleeding accompanying follicle growth and an increase in serum estradiol levels, was achieved in all patients (100%) within 6 months after transplantation. The median time to menstrual resumption was 3 months in the study cohort. No patient was lost to follow-up.

When compared with the previous control group, no significant difference was observed in the rate of menstrual resumption (100% vs 73·7%; p = .3). However, the time to menstrual resumption was significantly shorter in the study cohort (3 months vs 4 months; p = .04; Table 3; Fig. 1). Notably, one patient in the study cohort achieved a spontaneous pregnancy 3 months following the procedure.

Discussion

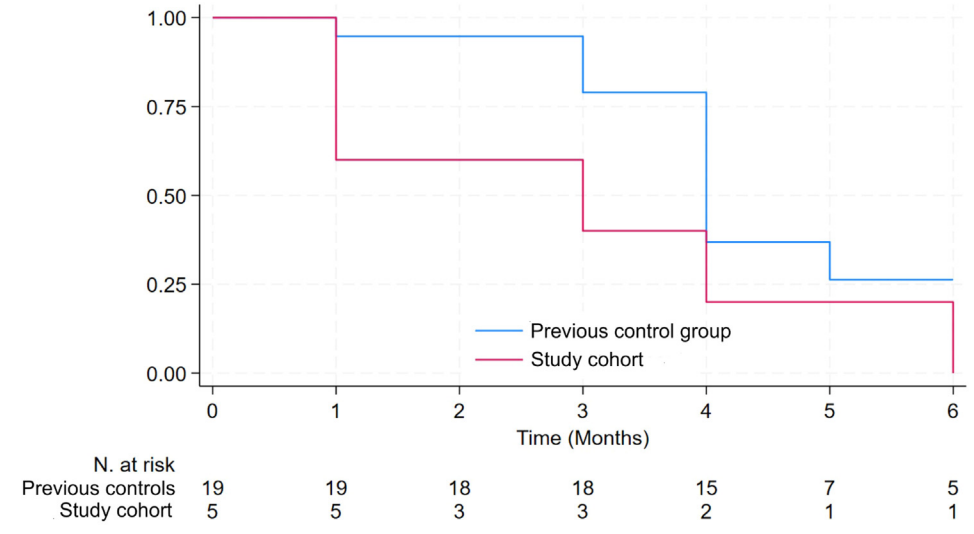
Main Findings

In this pilot clinical study, OTT combined with autologous PRP appeared safe and feasible. No adverse reactions or surgical complications were observed, and operative time in the study cohort was comparable to that of previous controls.

In terms of early effectiveness, the addition of PRP to OTT resulted in a rate of menstrual resumption comparable to that of standard OTT, with a significantly shorter time to recovery of ovarian function.

Fig. 1

Kaplan−Meier curves showing time to menstrual resumption of menstrual cycles within the first 6 months after ovarian tissue transplantation in the study cohort (PRP group) and the previous controls (non-PRP group).



Findings, Interpretation, and Comparison with the Literature

Several factors contribute to follicular loss and failure of procedure of OTC and OTT, including mechanical damage during tissue harvesting, the transitory ischemic window following transplantation, inflammatory responses, and cellular stress related to the freeze−thaw process. Among these, delayed revascularization of the graft remains one of the main determinants of early follicular depletion and reduced graft longevity.

Accordingly, several pharmacological and biological strategies have been investigated to mitigate ischemic injury and preserve follicular survival following OTT (Table 4) [21].

Among antioxidant approaches, *N*-acetylcysteine has shown promising results. In murine models, Mahmoodi et al and Olesen et al demonstrated a reduction in apoptosis and improved the primordial follicles survival [22,23].

Regenerative strategies using stem cells have also been explored. Xia et al reported enhanced angiogenesis and folliculogenesis following the use of mesenchymal stem cells, while Manavella et al observed similar effects using adipose-derived stem cells in ovarian cortical strips [24,25].

Targeted angiogenic factors have also been evaluated as well. Gao et al and Tanaka et al demonstrated that basic fibroblast growth factor promotes angiogenesis and follicle survival after transplantation [26,27]. Similarly, Ma et al showed that follicle-stimulating hormone preconditioning improved vascular density in transplanted tissue, although this did not translate into increased follicle survival [27,28].

Several pharmacological agents with potential protective effects against ischemic damage have also been studied. Saber et al investigated vitamin E, sphingosine-1-phosphate, simvastatin, and methylprednisolone, reporting variable reductions in cellular damage, but limited evidence of consistent primordial follicle preservation. Verapamil, a calcium channel blocker, was associated with improved primordial follicle survival, although its mechanism remains incompletely understood [29]. Conversely, despite initial hypotheses, GnRH agonists have not demonstrated protective effects and may even exacerbate follicular depletion.

In this context, PRP has garnered growing interest due to its regenerative and pro-angiogenic properties. Upon activation, platelets release a complex milieu of growth factors, cytokines, chemokines, and adhesion molecules involved in angiogenesis, inflammation modulation, and tissue repair [30]. However, preclinical evidence on PRP remains conflicting. Shojafar et al and Sanamiri et al reported improved follicle viability and neovascularization in murine ovarian auto-transplanted models using PRP derived from adult and umbilical cord blood, respectively [31,32]. In contrast, Subiran Adrados et al [33] did not observe significant improvements in vascularization or follicular survival in xenotransplanted human ovarian tissue. These discrepancies may reflect differences in PRP composition, concentration, activation methods, and dosing.

Importantly, most of the above strategies, including PRP, have been evaluated primarily in animal models. In contrast, the present study represents, to our knowledge, the first clinical investigation of PRP use in vivo in women undergoing OTT.

Clinical Implications and Endocrine Recovery

The present study was designed as the first phase of a multiphase clinical trial, with safety as the primary endpoint and early effectiveness as a secondary outcome.

In this context, endocrine recovery was operationally assessed through menstrual resumption, which represents an early clinical marker of ovarian endocrine activity rather than a comprehensive evaluation of long-term ovarian function.

Although the addition of PRP did not change the overall rate of menstrual resumption, the observed reduction in time to cycle recovery may reflect faster graft revascularization and earlier restoration of endocrine activity. These findings should be interpreted as preliminary and hypothesis-generating, pending confirmation through long-term follow-up and reproductive outcomes.

A subsequent phase of the study is currently ongoing and aims to evaluate the duration and stability of menstrual recovery, endocrine function over time, and reproductive

Table 4

Agents tested for reducing ischemic injury during the post-transplantation phase in animal studies.

Substance	Mechanism	Impact on PMF Reserve	Graft Species	Study
Erythropoietin	Antioxidant	Increased PMFs (28 d)	Mouse	Mahmoodi et al [34]
N-acetylcysteine	Antioxidant	Increased PMFs (28 d)	Mouse	Mahmoodi et al [23]
Stem cells	Angiogenesis	Increased PMFs (21 d)	Human	Xia et al [24]
Stem cells	Angiogenesis	Increased PMFs (7 d)	Human	Manavella et al [25]
bFGF	Angiogenesis	Increased PMFs (7 d)	Mouse	Gao et al [26]
bFGF	Angiogenesis	Increased PMF (6 wk)	Human	Tanaka et al [27]
FSH	Angiogenesis	No assessment of PMF numbers	Mouse	Ma et al [28]
Verapamil	Ca channel blocker	Increase PMFs (2 wk)	Mouse	Saber et al [29]
GnRH agonist	Anti-apoptosis	Decrease in PMFs (15 wk)	Human	Maltaris et al [35]

outcomes, including pregnancy and live birth rates, to better define the long-term clinical utility of PRP in this setting.

Strengths and Limitations

A major strength of this study is its innovative prospective design, representing the first clinical application of PRP in cryopreserved ovarian tissue.

Nevertheless, several limitations must be acknowledged. PRP preparation protocols, concentration, and modes of administration are not yet standardized, and in this pilot study, PRP was applied through multiple modalities (tissue bathing, platelet gel embedding). Consequently, the relative contribution of each component, the relative contribution of calcium gluconate−induced gel formation, cannot be independently assessed.

Moreover, the absence of a PRP-only control arm does not allow discrimination between the effects of PRP on residual ovarian tissue and those on transplanted ovarian fragments.

The absence of group matching and covariate adjustment, and limited sample size may have introduced potential biases, and restricts generalizability. Finally, the short follow-up does not allow assessment of long-term endocrine stability, graft longevity, or fertility outcomes. These limitations are being addressed in the ongoing long-term phase of this research project.

Conclusion

The addition of autologous PRP to cryopreserved ovarian tissue during OTT appears safe and feasible. Preliminary data suggest that PRP may accelerate early graft functional recovery as reflect by a shorter time to menstrual resumption. These results provide the rational for lager, long-term, and controlled studies to validate the clinical impact of PRP on endocrine and reproductive outcomes.

Attestation Statement

The subjects in this trial have not concomitantly been involved in other trials. Data regarding any of the subjects in the study have not been previously published unless specified. Data will be made available to the editors of the journal for review or query upon request. The appropriate checklist for this study design (CONSORT: The Consolidated Standards of Reporting Trials statement) was followed.

Data Availability

Individual participant data will be available. All of the individual participant data collected during the trial, after deidentification, will be shared upon request. Study protocol, statistical analysis plan, informed consent form, clinical study report, analytic code will be available as well. All these data will be immediately available following publication, with no end date, to all researchers who provide a methodologically sound proposal.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.jmig.2026.01.061.

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