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A multicenter, prospective sibling oocyte study revealed that HyperSpermTM improves the number and quality of embryos in patients undergoing in vitro fertilization

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Abstract

Background Assisted reproductive technologies (ART), including in vitro fertilization (IVF), have transformed the treatment of infertility; however, success rates remain suboptimal. HyperSperm is a novel capacitation technology designed to enhance sperm function by promoting hyperactivation without compromising acrosomal integrity or sperm viability. Previous studies have shown that HyperSperm improves human sperm motility parameters and increases embryo development in mice and humans, as well as implantation rates in mice. The present study aimed to evaluate the clinical utility of HyperSperm in IVF.

Methods A prospective sibling oocyte study was conducted in 41 IVF patients (ClinicalTrials.gov identifier: NCT05680363). Semen samples from each patient were divided and processed using either standard preparation protocols or the HyperSperm protocol. Fertilization outcomes, embryo development, blastocyst formation, embryo quality, and euploidy rates assessed by preimplantation genetic testing for aneuploidy (PGT-A) were compared between conditions.

Results HyperSperm treatment was associated with significantly higher blastocyst development rates compared with standard preparation (55.6% vs. 47.9%, $p = 0.0038$), resulting in a greater number of blastocysts per cycle. Moreover, embryos generated following HyperSperm treatment exhibited improved morphological quality and a higher euploidy rate as determined by PGT-A.

Conclusions HyperSperm improves key developmental outcomes in IVF, increasing blastocyst yield, embryo quality, and chromosomal normality. These findings support the translational potential of HyperSperm as a clinically relevant strategy to enhance early embryo competence and improve IVF efficiency.

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Key words Assisted reproduction technology, Capacitation, Time-lapse, Sperm

Introduction

Assisted reproductive technologies (ART), including in vitro fertilization (IVF), have transformed infertility treatment, yet the efficiency of these procedures remains suboptimal [1]. One critical factor influencing ART outcomes is the quality and functional state of the sperm used for fertilization [2]. In clinical practice, methods of semen preparation such as swim-up, density gradient centrifugation or other selection devices are routinely used to select motile sperm for assisted reproductive procedures; however, these approaches remain largely based on conventional parameters such as motility and morphology and often fail to fully capture the functional competence of sperm. In particular, sperm capacitation, a complex maturational process required for fertilization, is not ensured by these preparation techniques. Despite its essential role in enabling sperm to undergo the acrosome reaction, interact with the oocyte, and achieve successful fertilization [3], this process is rarely assessed despite its essential role. Optimization of sperm processing protocols is therefore a key strategy to improve ART outcomes, particularly in IVF, where sperm function must both support oocyte penetration and contribute to subsequent embryo development.

In previous studies, we introduced HyperSperm, a novel capacitation medium designed to enhance sperm function by promoting hyperactivation without compromising acrosomal integrity [4]. We showed that HyperSperm improved motility parameters without affecting sperm viability, both in donors [4] and patients attending IVF clinics [5]. To further evaluate its functional impact, we conducted parallel studies in a mouse model. In both humans and mice, HyperSperm treatment led to a significant increase in embryo development rates [4], indicating that its benefits extend beyond fertilization to support early embryogenesis. Moreover, in mice, we observed higher implantation rates following the use of HyperSperm-treated sperm [4], suggesting a potential improvement in embryo competence, an effect that remains to be explored in human clinical settings.

Here, we tested HyperSperm's safety and efficacy in a broader population of patients attending fertility clinics and evaluated advanced developmental parameters such as embryo ploidy.

Materials and methods

Study design and participants

This was a prospective, multicenter, sibling oocyte study (ClinicalTrials.gov ID: NCT05680363) including 41 couples attending 3 clinics between August 2023 and December 2025. The study was approved by the Ethics

Committee of IBYME-CONICET (Ref: CE001/April 2019); and participants provided written consent to be included in the study. A flowchart of study progression is shown in Fig. 1. Inclusion criteria were women aged 20–41 years with an ovarian reserve of 6–30 antral follicles and men aged 20–55 years, with the following sperm parameters: sperm concentration $\geq 10 \times 10^6/\text{mL}$, total motility $\geq 20\%$, normal morphology (Kruger criteria) $\geq 3\%$. Exclusion criteria for women included sexually transmitted infection (STI), diabetes or other metabolic diseases, repeated pregnancy loss (>2 clinical pregnancies without live birth), or 2 or more failed ART cycles. Exclusion criteria for men were any diagnosed STI, or previous IVF failure. The primary outcome was blastocyst rate, and secondary outcomes were fertilization rate and embryo quality. In addition, euploidy rates were assessed in blastocysts undergoing PGT-A, and biochemical and clinical pregnancy outcomes were recorded after embryo transfer.

Semen samples and processing

Semen samples of 41 patients were obtained by masturbation into sterile containers and processed within 1 hour of collection. Semen samples were divided into two halves for Control (the clinic standard sperm preparation procedure) and HyperSperm (treatment). Sperm were isolated either by density gradient centrifugation using PureSperm (Nidacon, Sweden) or SpermGrad (Vitrolife, Sweden), or by swim-up using PureSperm Wash (Nidacon, Sweden), depending on the protocols of each participating clinic. Control sperm were incubated in either Human Tubal Fluid (modified HTF) medium (FUJIFILM Irvine Scientific, USA) supplemented with 3% HSA (Human serum albumin, FUJIFILM Irvine Scientific) at 25 °C, or GMOPSTM (Vitrolife, Gothenburg, Sweden) at 37 °C, for up to 4 hours. In the Treatment group, sperm were processed according to HyperSperm protocol [4]. HyperSperm is a proprietary formulation whose mechanism of action is centered on fine-tuning intracellular Ca^{2+} dynamics.

Ovarian stimulation and oocyte retrieval

Controlled ovarian stimulation was performed according to each clinic standard protocol and clinician recommendation, through gonadotropin-based regimens, either GnRH antagonist based or progestin-primed ovarian stimulation (PPOS) protocols. Recombinant FSH (folitropin alfa; Gonal-F, Merck S.L., Argentina; Folitime, GemaBiotech, Argentina; or Recovelle, Ferring, Argentina) was administered alone or in combination with LH activity, provided as recombinant LH (lutropin alfa;

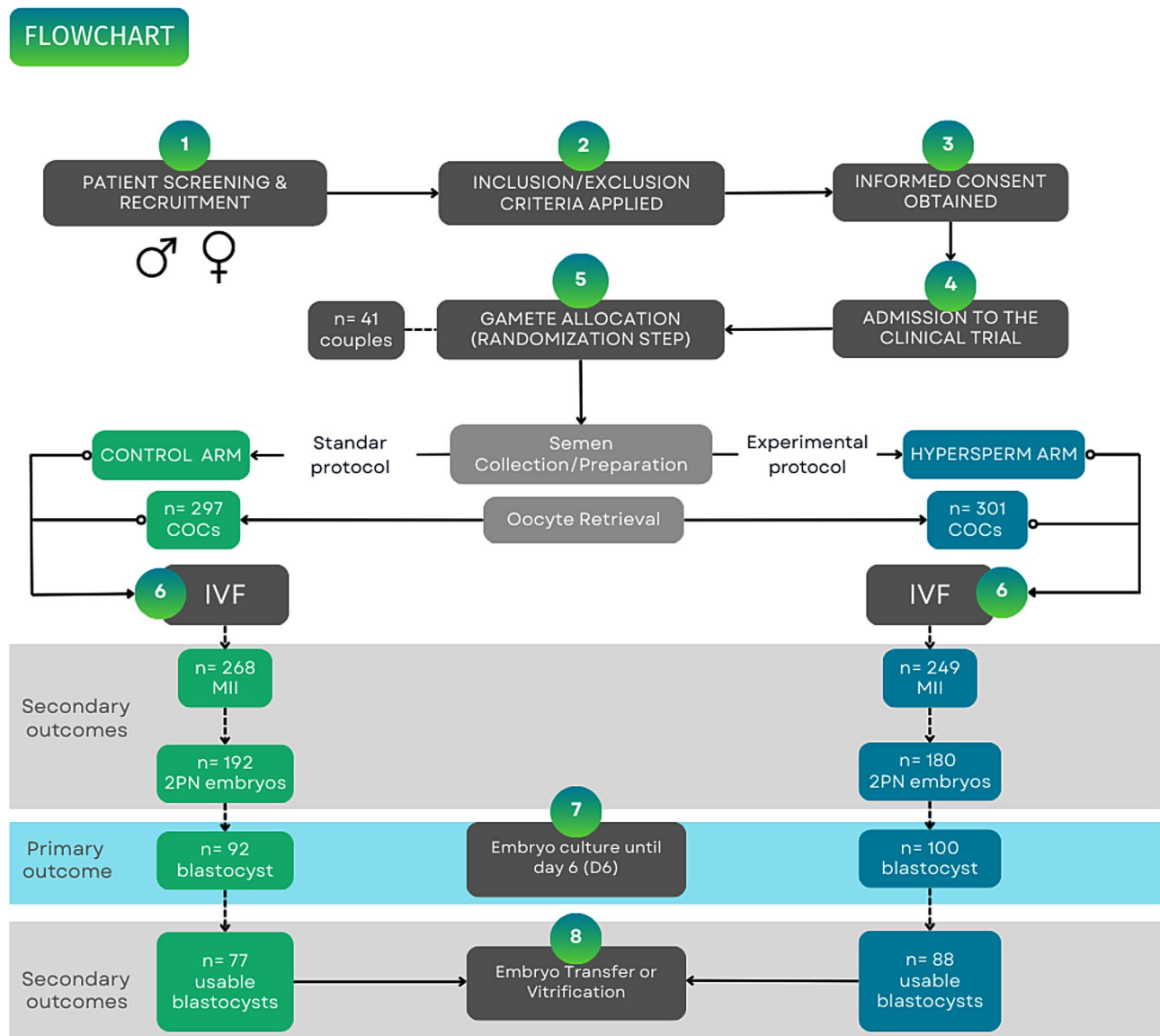


Fig. 1 Workflow diagram of the clinical trial. After recruitment and consent, eligible patients underwent controlled ovarian stimulation. Retrieved oocytes were randomly allocated into two groups according to the sperm preparation method applied: control (standard protocol) and HyperSperm (experimental protocol). Following fertilization and embryo culture, embryos were assessed, and transferred or cryopreserved according to clinical criteria. Outcomes were evaluated for each arm. COCs: cumulus oocyte complex; MII: metaphase II oocytes; 2PN: two pronuclei

Pergoveris, Merck S.L.) or human menopausal gonadotropin (hMG; Menopur, Ferring; or Lifecell, Biosidus, Argentina). In some cases, adjuvant agents such as clomiphene citrate were included. Pituitary suppression was achieved with GnRH antagonists (cetrotrex acetate, Cetrotide, Merck S.L.; or ganirelix acetate, Orgalutran, Organon, Argentina) or with progestins in the context of PPOS protocols (progesterone, Geslutin, Ferring; or desogestrel, Organon). Final oocyte maturation was triggered with recombinant hCG (Ovidrel, Merck S.L.), GnRH agonist, or a combination. Oocyte retrieval was performed 36h after triggering by ultrasound-guided transvaginal follicular aspiration.

In vitro fertilization

Classic IVF was performed in 50 or 500 µl of IVF medium G-IVF Plus™ (Vitrolife) or Global Total LP for Fertilization (LifeGlobal, CooperSurgical, United States), supplemented with 3–6% human serum albumin (FUJIFILM Irvine Scientific) under mineral oil OVOIL™ (Vitrolife). Collected cumulus–oocyte complexes (COCs) were divided in two halves. In cases where an odd number of COCs was obtained, the extra COC was randomly assigned to one of the two groups. COCs were inseminated either with Control or HyperSperm-treated sperm and incubated at 37 °C and 6% CO₂ during 4 hours. The number of fertilized eggs (i.e., with two pronuclei, 2PN)

was recorded the following morning (18–20 hours after insemination). Fertilization rate was calculated after excluding immature or atretic oocytes on D1 as the percentage of 2PN per mature oocyte.

Embryo culture and time lapse monitoring

Fertilized eggs were cultured in the incubator for 5–6 days to blastocyst stage. Cells were incubated individually in Global® Total® LP (LifeGlobal, CooperSurgical) under mineral oil OVOIL™ (Vitrolife) at 37 °C, and under 6% CO₂ and 5% O₂ atmosphere. Blastocysts' quality was assessed using the Gardner grading system [6]. The number of total blastocysts and utilizable blastocyst [7] at day 5 and day 6 were recorded. The rate was calculated as the percentage of blastocysts per fertilized egg. Utilizable blastocysts were either vitrified or transferred fresh. All transfer were single embryo transfers.

In 7 IVF cycles, fertilized eggs were cultured in Esco Miri® TL (Esco Medical, Denmark) incubator for time-lapse monitoring. Time-lapse monitoring allowed the determination of the time of each developmental event: tPNf (time of pronuclei fading); t2 (time to 2 cells); t3 (time to 3 cells); t4, (time to 4 cells); t5 (time to 5 cells); t6 (time to 6 cells); t7 (time to 7 cells); t8 (time to 8 cells); tM (time to morula); tB (time to blastocyst); cc2 (duration of the second cell cycle); cc3 (duration of the third cell cycle); s2 (time to complete synchronous division).

Preimplantation genetic testing for aneuploidies (PGT-A)

In 15 IVF cycles, blastocysts with an adequate expansion grade and a clearly identifiable trophectoderm (TE) layer were utilized for embryo biopsy using a laser-assisted hatching system. A small opening was created in the zona pellucida, and 5–10 TE cells were gently aspirated and removed using a micromanipulation pipette. Biopsied blastocysts were immediately vitrified according to established cryopreservation protocols. Each TE biopsy was transferred into a sterile, DNA-free PCR tube containing a lysis buffer. Whole genome amplification was carried out by the company Igenomix (Argentina). Amplified DNA was quantified and assessed for quality before proceeding to genetic analysis. Aneuploidy screening was performed using next-generation sequencing (NGS). For NGS-based analysis, amplified DNA libraries were sequenced on an Illumina MiSeq/NextSeq. Bioinformatic analysis was conducted using the Ion Reporter™ Server System (Thermo Fisher, USA). Embryos were classified as euploid, aneuploid, mosaic, or undetermined based on established clinical thresholds for copy-number deviation and mosaicism levels.

Statistical analysis

All statistical evaluations were carried out with GraphPad Prism 6 (GraphPad Software, La Jolla, CA, USA).

In this sibling-oocyte design, the primary unit of analysis for fertilization and embryo development outcomes was the donor (cycle). Fertilization rate, blastocyst rate, and usable blastocyst rate were calculated for each donor under both Control and HyperSperm conditions, and paired comparisons were performed using the Wilcoxon signed-rank test. This approach accounts for the non-independence of oocytes originating from the same donor and preserves the paired nature of the experimental design. For descriptive purposes, outcomes are also presented as aggregated counts and percentages at the oocyte or embryo level; however, these were not treated as independent observations for statistical testing. Categorical outcomes such as embryo quality and euploidy rates were analyzed using Chi-square or Fisher's exact tests at the embryo level. These analyses are considered exploratory and do not account for within-donor clustering. Time-to-event analyses of embryonic development were performed using the log-rank (Mantel–Cox) test. Statistical significance was defined as a two-tailed *p* value < 0.05.

Results

Baseline demographic and clinical characteristics of the study population are summarized in Table 1. A total of 598 COCs were retrieved and randomly allocated to the Control (*n* = 297) or HyperSperm (*n* = 301) arms. Each group was inseminated accordingly with control or HyperSperm-treated sperm, and fertilization was assessed the next day. After fertilization, there were 29 and 52 immature or atretic oocytes on D1 in the Control and HyperSperm group, respectively.

Fertilization rate were comparable between Control and HyperSperm groups (71.6% vs 72.3%) (Table 2), while the blastocyst rate was higher in the HyperSperm group (47.9% vs 55.6%, *p* = 0.0038), as was the utilizable blastocyst rate (40.1% vs 48.9%, *p* = 0.0104) (Table 3). Importantly, HyperSperm increased the number of blastocyst available for transfer in 24 out of 41 cases. Notably, in 9 cases, no blastocysts were obtained in the control arm while the HyperSperm arm resulted in at least 1 blastocyst in 5 of these cases.

Sperm treated with HyperSperm showed a higher proportion of good-quality blastocysts (grade AA) compared with Control, although this difference did not reach statistical significance (Fig. 2A). In addition, PGT-A analysis performed on a subset of embryos (32 control-derived and 32 HyperSperm-derived embryos) showed a higher euploidy rate in the HyperSperm group compared with controls (31.3% vs. 53.1%, *p* = 0.13) (Fig. 2B), although the study was not designed to detect statistically differences in euploidy rates.

In a subset of 12 patients, embryo development was monitored by time-lapse imaging, with a total of 17

Table 1 Clinical characteristics and semen parameters of the study population

Parameters	
Female age, years	36.4 ± 3.6 (27–42)
Male Age, years	38.2 ± 4.6 (30–55)
Duration of infertility, years	2.8 ± 2.3 (0.5–15)
Primary cause of infertility, % (n/N)	
Female	43.9 (18/41)
Tubal factor	44.4 (8/18)
Polycystic Ovary Syndrome	16.7 (3/18)
Endometriosis	16.7 (3/18)
Others	22.2 (4/18)
Male	4.9 (2/41)
Combined	7.3 (3/41)
Unexplained	43.9 (18/41)
Previous IVF cycles, % (n/N)	
0	61.0 (25/41)
1	24.4 (10/41)
2	14.6 (6/41)
Ovarian Stimulation Protocols, % (n/N)	
Gonadotropins	4.9 (2/41)
Gonadotropins + GnRH antagonist protocol	68.3 (27/41)
Gonadotropins + progestin-primed ovarian stimulation	26.8 (11/41)
Number of COCs	14.7 ± 5.9 (7–28)
Number of MII	12.6 ± 5.0 (4–24)
Semen parameters	
Semen volume, ml	2.8 ± 1.4 (1.0–6.6)
Sperm concentration, 10 ⁶ per mL	99.3 ± 40.6 (15–225)
Total sperm number, 10 ⁶	263.9 ± 173.2 (74–1080)
Total motility, %	63.1 ± 13.5 (22–88)
Progressive motility, %	54.8 ± 13.3 (12–75)
Sperm morphology normal forms, %	7.3 ± 3.8 (3–17)
Sperm DNA fragmentation, %	11.7 ± 6.8 (2–26)

Data from *n* = 41 couples. All values are expressed as mean ± standard deviation (min–max), except for the primary cause of infertility and ovarian stimulation protocols, which are presented as percentage (% (n/N)). The causes of infertility are classified as female, male, combined, or unexplained. GnRH, Gonadotropin-Releasing Hormone. PPOS, progestin-primed ovarian stimulation. COCs, cumulus-oocyte complexes. Values correspond to semen analyses performed prior to the IVF cycle in 41 patients, except for parameter sperm morphology normal forms, (*n* = 36) and sperm DNA fragmentation (*n* = 24)

embryos in the control group and 20 embryos in the experimental group. The resulting morphokinetic parameters are summarized in Table 3. Overall, no significant differences were detected between the two groups, consistent with our previous findings [4].

To date, 25 embryo transfers using embryos generated with HyperSperm-treated sperm have resulted in eight biochemical pregnancies. Six of these progressed to confirmed clinical pregnancies, with outcomes still pending in some cases. Three healthy live births have been reported to date.

Table 2 Embryo data following IVF with sperm treated with standard procedures (Control) or HyperSperm in 41 couples

Parameters	Control	HyperSperm
Number of COCs per arm	297	301
Rate of maturity (MII/COCs)	90.2% (268/297)	82.7% (249/301)
Fertilization rate (2 PN embryos/MI)	71.6% (192/268)	72.3% (180/248)
Blastocyst rate (blastocyst/2 PN embryos)	47.9% (92/192)	55.6% (100/180) **
Usable blastocyst rate (usable blastocysts/2 PN embryos)	40.1% (77/192)	48.9% (88/180) *

Values are presented as % (n/N). COCs, cumulus-oocyte complexes. 2PN, 2-pronuclear embryos. Comparisons between the control and HyperSperm groups were performed using the Wilcoxon signed-rank test. * *p* < 0.05, ** *p* < 0.01 was considered statistically significant

Table 3 Morphokinetics parameters of embryo development in Control and HyperSperm groups

Parameters	Control	HyperSperm
t2 (h)	31.8 (27.1–34.0)	29.5 (27.1–33.7)
t3 (h)	39.5 (37.0–41.1)	39.4 (36.0–40.5)
t4 (h)	41.8 (39.8–47.3)	41.8 (40.7–48.3)
t5 (h)	52.4 (51.5–55.1)	52.4 (51.8–55.4)
t6 (h)	55.4 (53.8–58.0)	56.3 (52.4–62.6)
t7 (h)	57.7 (55.8–64.1)	58.6 (55.3–63.4)
t8 (h)	60.8 (56.8–64.8)	60.6 (57.9–67.1)
tM (h)	89.4 (82.8–96.3)	87.3 (83.4–95.7)
tB (h)	108.8 (104.5–113.3)	109.4 (104.2–115.9)
cc2 (h)	9.0 (8.0–11.7)	10.6 (4.4–11.1)
cc3 (h)	14.0 (11.6–16.0)	13.0 (11.6–19.0)
s2 (h)	0.7 (0.3–4.6)	2.2 (0.6–6.0)

Time to 2 (t2), 3 (t3), 4 (t4), 5 (t5), 6 (t6), 7 (t7), 8 cells (t8), morula (tM) or blastocyst (tB), duration of the second (cc2=t3–t2) and third cell cycle (cc3=t5–t3), and synchronization of the second cell division (s2=t4–t3). Values expressed as median (interquartile range) and analyzed with the log-rank test (Mantel-Cox); n.s., *n* (Control)=17 embryos, *n* (HyperSperm)=20 embryos

Discussion

Our original proof-of-concept study [4] evaluated the effects of a novel sperm preparation technique, HyperSperm, using donated oocytes in a split oocyte design. While that work demonstrated significantly higher utilizable blastocyst rates under the new method, the use of donor oocytes limited the generalizability of the results. Here, we investigated whether HyperSperm could provide the same benefits to patients undergoing IVF with their own oocytes, enhancing real world relevance by including a wider range of oocyte quality and patient-specific factors, thereby allowing for a more accurate assessment of HyperSperm performance in routine IVF settings.

Sperm capacitation is a tightly regulated and inherently inefficient process, with only a small subset of the ejaculated sperm population acquiring fertilization competence under physiological conditions [8]. This inefficiency is amplified in vitro, where capacitating media

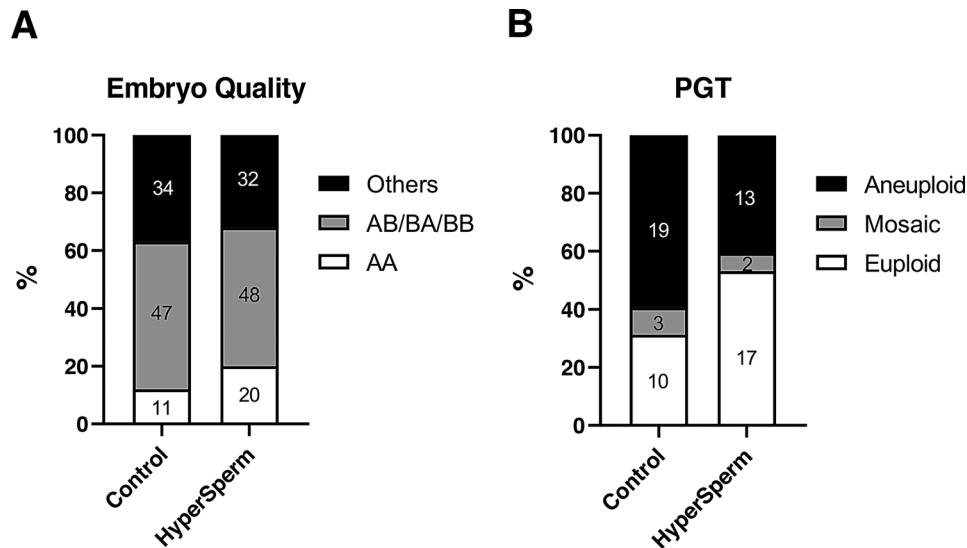


Fig. 2 Embryo quality and chromosomal status. **(A)** Distribution of blastocyst quality grades between the Control ($n=92$ embryos) and HyperSperm ($n=100$ embryos) groups. Embryo quality was classified into three categories: AA (highest-quality blastocysts), AB/BA/BB (intermediate quality), and others (all remaining morphological grades). **(B)** Preimplantation genetic testing for aneuploidy (PGT-A) outcomes expressed as percentages of euploid, mosaic, and aneuploid embryos in both groups. (Control, $n=32$ embryos; HyperSperm, $n=32$ embryos)

fail to fully replicate the complex and dynamic environment of the female reproductive tract [9]. In this context, the improvement in embryo development observed with HyperSperm likely reflects a more precise modulation of capacitation, which in turns increases the fraction of sperm achieving a capacitated, fertilization-competent state without prematurely triggering acrosomal exocytosis [4, 5].

This targeted enhancement likely contributes not only to improved fertilization rates but also to the developmental potential of resulting embryos, underscoring the central role of fine-tuned capacitation in optimizing assisted reproduction outcomes. Emerging evidence indicates that beyond delivering the haploid genome [10], sperm contribute a complex repertoire of epigenetic marks, RNAs [11], and proteins that can be transmitted to the oocyte and may influence early embryo gene regulation and developmental trajectories. These sperm-borne signals include specific DNA methylation and histone modifications, small non-coding RNAs, and proteins involved in chromatin remodelling [12], which have been implicated in preimplantation development and may underlie subtle differences in embryo competence observed in ART settings.

Embryos generated from HyperSperm-treated sperm showed a higher proportion of euploidy in a subset of blastocysts undergoing trophectoderm biopsy and PGT-A analysis. While this observation should be interpreted with caution, it could suggest that HyperSperm may influence aspects of sperm quality in ways that extend beyond conventional motility or morphology parameters. One plausible explanation is that the

treatment may selectively enrich sperm with lower levels of DNA fragmentation and oxidative damage, both of which are known contributors to post-fertilization chromosomal instability. However, no large overall differences in the proportion of DNA-fragmented sperm were observed following HyperSperm treatment in our previous study, despite the presence of a modest reduction [5]. Whether HyperSperm treatment reduces oxidative stress in sperm remains to be determined, although this seems unlikely given that the control samples did not exhibit clear signs of oxidative damage, such as impaired motility or reduced viability. Alternatively, HyperSperm may improve sperm function in ways that support early embryonic development and chromosomal stability. Given that the majority of embryonic aneuploidies are of maternal origin, it is also conceivable that improved sperm preparation during the HyperSperm treatment may preferentially support the developmental competence of chromosomally normal oocytes, thereby increasing the likelihood of generating euploid embryos. While the underlying mechanisms remain unclear, these observations warrant further investigation.

We acknowledge some limitations of the current study: The participants' cohort was limited in number. That said, the use of a sibling-oocyte split design, together with the high degree of consistency observed across different patients, supports the interpretation that the differences in embryo developmental outcomes are attributable to HyperSperm treatment rather than to inter-patient variability. If validated in larger cohorts, the addition of HyperSperm could offer a simple and effective tool to increase IVF outcomes. Future research should expand

on these promising results by evaluating long-term outcomes such as implantation success, pregnancy rates and neonatal health, alongside mechanistic studies investigating how fertilization methods, media composition, and handling techniques intersect to drive improved embryo quality.

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Author contributions

NO, MDGE, GML and CBG performed the experiments and analyzed data. CB, MH, MP, EDM, MA, ML, CC, VTM and EN discussed results and contributed with samples and resources. NO, MDGE, MGB and DK analyzed and interpreted the patient data. MGB and DK wrote the paper with contributions of all coauthors. MDGE, MGB and DK designed the study.

Funding

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Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of IBYME-CONICET (Ref: CE001/April 2019), and the clinical trial was registered at ClinicalTrials.gov (NCT05680363). All patients provided written informed consent. The study was carried out in accordance with institutional guidelines and the ethical principles of the Declaration of Helsinki (1964) and its subsequent amendments.

Consent for publication

Not applicable.

Competing interest

MGB, DK, GML and MDGE are shareholders of Fecundis. GML is a member of the Editorial Board of *Journal of Translational Medicine*. GML was not involved in the review or editorial process for this paper, on which she is listed as an author. The rest of the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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