Received: 21 June 2019 | Accepted: 1 August 2019

DOI: 10.1111/and.13403

ORIGINAL ARTICLE

First International Journal of Andrology
ANDROLOGIA WILEY

Does a microfluidic chip for sperm sorting have a positive add-on effect on laboratory and clinical outcomes of intracytoplasmic sperm injection cycles? A sibling oocyte study

Ender Yalcinkaya Kalyan[1] | Seren Can Celik[2] | Ozlem Okan[3] | Gulden Akdeniz[3] | Seda Karabulut[4] | Eray Caliskan[2]

[1]Adatip Hospital Assisted Reproduction Unit, Istanbul, Turkey

[2]Okan University Hospital Assisted Reproduction Unit, Istanbul, Turkey

[3]Adatip Hospital Assisted Reproduction Unit, Sakarya, Turkey

[4]International School of Medicine, Regenerative and Restorative Medicine Research Center (REMER), Medipol University, Istanbul, Turkey

Correspondence
Ender Yalcinkaya Kalyan, Adatip Hospital Assisted Reproduction Unit, Istanbul, Turkey.
Email: endersu81@gmail.com

Abstract

The most recent technologies for sperm sorting involve microfluidics. However, the most important question whether their use is of any advantage in terms of laboratory and clinical IVF/ICSI outcomes still remains controversy. In this study, we aimed to investigate whether a microfluidic sperm sorting device (Fertile Plus®) has a positive add-on effect on laboratory and clinical outcomes. Sibling oocytes of 81 patients were assigned to two sperm sorting groups including swim up and Fertile Plus®. All embryos were cultured until day 5/6. Fertilisation, embryo quality and blastocyst development were assessed as primary outcomes among 81 patients; clinical pregnancy, implantation and live birth rates were analysed as secondary outcomes as a subgroup analysis due to transfer cancellations. No statistically significant differences were found between groups in terms of all outcomes analysed in laboratory and clinical terms ($p > .05$ for all). The results of this study suggest that sorting spermatozoa through Fertile chip does not improve laboratory outcomes significantly and does not seem to have a positive contribution to clinical outcomes.

KEYWORDS

chip, implantation, intracytoplasmic sperm injection, microfluidic, sibling

1 | INTRODUCTION

Although intracytoplasmic sperm injection (ICSI) historically appeared as a promising technique for overcoming male factor infertility, its use has been reported to increase globally also in case of nonmale factor infertility without a clear evidence supporting its benefits (Boulet et al., 2015; Rosenwaks & Pereira, 2017). The increased use of ICSI revealed the importance of better sperm selection during the procedure. Currently, selection of sperm cells during ICSI is restricted to a few number of criteria such as motility and morphology under high magnification. Therefore, it is important to create a pool of spermatozoa including cells with the highest quality and competence by using better methods to sort them from the semen before ICSI. This will definitely increase the chance of choosing and injecting better spermatozoa and getting better outcomes.

Besides conventional sorting methods including swim up and density gradient centrifugation, there are currently used sperm sorting and selection techniques which have been used in clinical IVF today. These methods mostly include techniques such as intracytoplasmic morphologically selected sperm injection (IMSI), magnetic-activated cell sorting (MACS) and physiologic intracytoplasmic sperm injection (PICSI). Although some promising preliminary results have been published regarding the use of these techniques (Dirican et al., 2008; Kim et al., 2014; Worrilow et al., 2013), recent reviews of the relevant clinical studies were insufficient to support their benefits in terms of clinical outcomes following IVF/ICSI (Avalos-Duran et al., 2018; Stimpfel, Verdenik,

 © 2019 Blackwell Verlag GmbH

Zorn, & Virant-Klun, 2018; Teixeira et al., 2013). Also, the results of a recent preclinical study reported improved ICSI outcomes through sperm selection by thermotaxis in mice (Perez-Cerezales et al., 2018).

The most recent technologies for sperm sorting involve microfluidics. These systems have been integrated into use in the field of assisted reproduction after they were converged into systems that can be used with larger volume samples (Chinnasamy, Behr, & Demirci, 2016; Samuel et al., 2018). In addition, there are clinical studies showing that spermatozoa processed with these chips yielded higher DNA integrity and lower DNA damage compared with conventional sorting techniques (Quinn et al., 2018; Schulte, Chung, Ohl, Takayama, & Smith, 2007). However, the most important question whether their use is of any advantage in terms of laboratory and clinical IVF/ICSI outcomes still remains controversy. In the literature, there is only one study evaluating clinical data following the use of a commercial microfluidic chip (Fertile Plus®; Koek Biotechnology) for ICSI cycles who were suffering from unexplained infertility; they found that a number of grade 1 embryos were found to be significantly higher in microfluidic group resulting in a higher rate of embryo freezing despite comparable fertilisation ratios (Yetkinel et al., 2019).

In this study, we aimed to investigate whether this microfluidic sperm sorting device has a positive add-on effect on total blastocyst development in the laboratory and on clinical outcomes such as clinical pregnancy rate (CPR) and live birth rate (LBR). To our knowledge, this is the first study that will report the differences between conventional swim-up technique and microfluidic chip by using a sibling oocyte setting.

2 | MATERIALS AND METHODS

2.1 | Participants

The data of the study were collected from 81 patients who admitted to two private IVF clinics in Turkey using similar laboratory conditions (such as culture media, consumables and equipment) for infertility treatment. Patient enrolment in the study was performed based on three main criteria on the day of oocyte pick up: these criteria were having an age <42 years and at least five MII oocytes for female patients. For the male patients, only the ones who had severe male factor (having at least one million motile spermatozoa/ml in the ejaculate) were excluded since these sperm sorting techniques were ineligible to sort sperm cells efficiently based on our previous practices. Besides, any male and female patients who were using medications due to an acute and/or chronic disease were not included in the study. There were no more exclusion criteria for female patients in terms of factors which were known to affect clinical outcomes such as presence of polys, uterine factor and myomas since patients having such aetiologies were directly assigned to total freezing at the beginning of the study. In addition, there were no preimplantation genetic diagnosis (PGD) cycles among the patients included in the study.

All patients who fulfilled inclusion criteria were informed about both sperm sorting methods routinely used in our clinic (swim up and Fertile Plus®). The couples who provided informed consent for all the procedures during their treatment were enrolled in the study. Ethics committee approval was taken from Non-interventional Clinical Research Committee of Medipol University, Istanbul, Turkey (no: 34162; date: 08/15/2018).

2.2 | Sperm sorting before ICSI

2.2.1 | Conventional swim up and Fertile Plus®

Semen was left to liquify for at least 20 min at room temperature before preparation. The number of spermatozoa was counted on a Makler chamber under a phase-contrast microscope. For all samples exceeding one million motile spermatozoa/ml, semen sample was aliquoted into two tubes. One ml from first aliquot was placed in a clean test tube, and 1 ml of sperm sorting media (Fertile Plus® sorting solution; KOEK Biotechnology) was directly put onto it in the swim-up method. Another 1 ml of semen was directly drained into Fertile Plus® chip through its hole by a micropipette tip. No centrifugation was performed in both techniques. Both were incubated under 37°C and 7.0% CO_2 around 15 min before ICSI, and sperm cells found in sorting media after 15 min were transferred to clean test tubes and kept under incubating conditions until ICSI. We modified the duration for sorting (that is recommended as 30 min for Fertile Plus® to yield higher number of spermatozoa with better DNA integrity) as 15 min. The reason of this modification was to create a more privileged pool for ICSI including sperm cells only with the highest performance since reduction in the number of sorted cells does not have so much significance for ICSI.

2.2.2 | Controlled ovarian hyperstimulation and ICSI

Ovarian stimulation and oocyte collection were performed as previously described by Ergin et al. (2014). The oocyte–cumulus complexes (COCs) collected were incubated in GIVF media (Vitrolife) supplemented with human serum albumin (HSA) until ICSI under the conditions of 37°C, 7% CO_2 and 7% O_2. After 2–3 hr, all oocytes were denuded and patients having at least five MII oocytes were enrolled in the study. MII oocytes of each patient were split equally into two; half of the sibling oocytes were microinjected with the spermatozoa sorted by conventional swim-up technique, and the other half were microinjected with the sperm cells sorted by Fertile Plus® (Koek Biotechnology). If the patient had odd number of MII oocytes, the extra one was assigned to swim-up group which was the routine sorting technique in our laboratories. Microinjected oocytes were left to incubate in protein-supplemented cleavage media (Sydney IVF) until fertilisation under the same incubating conditions.

2.2.3 | Assessment of fertilisation and cleavage

Fertilisation check was done after 18–22 hr of ICSI. All fertilised oocytes were transferred to fresh cleavage medium after fertilisation

assessment. The cleavage of the embryos was checked for once in the morning of day 2 (around 42–44 hr post-ICSI). Embryos which had more than 2 and equal size of blastomeres having ≤15% fragmentation were accepted as good quality embryos. If the patient had at least three good quality embryos in total on day 2, blastocyst transfer was planned. If not, that patient underwent an embryo transfer on day 3 and was withdrawn from the study.

All cleavage-stage day 2 embryos were transferred to protein-supplemented blastocyst media (Sydney IVF) in the afternoon and left to develop until days 5/6.

2.2.4 | Blastocyst culture and embryo transfer

Blastocyst transfer was planned for each patient in the study who had at least three good quality embryos on day 2. All embryos were incubated under the same conditions (37°C, 7% CO_2 and 7% O_2) up to day 5 until transfer. All fresh embryo transfers were performed on day 5. All patients underwent double embryo transfers from either group, and the assignment of transfers to groups was done consecutively according to their oocyte pick up times. In case that there were not two good quality blastocysts in the assigned group, transfers were performed from the other group or using blastocyst including one from each. Therefore, these patients were excluded from the analysis of clinical outcomes since implantation of each blastocyst was not clear in the circumstance that two embryos from different groups were resulted in one clinical sac. Besides, a total of 25 patients (11 patients in swim-up group and 14 patients in Fertile chip group) did not undergo a fresh embryo transfer due to the factors such as ovarian hyperstimulation (OHSS) risk among seven patients in swim-up group and 11 patients in chip group; due to higher progesterone levels on transfer day among one patient and presence of myoma among two patients in swim-up group; and due to thin endometrium in one patient in swim up and three patients in chip group; these patients were also excluded from the analysis of clinical outcomes.

All good quality blastocysts except the ones transferred were vitrified on days 5 and 6. Blastocyst scoring was done according to the classification system of Gardner & Schoolcraft (Gardner & Schoolcraft, 1999).

2.3 | Statistical analysis

All the statistical analyses in the study were performed by SPSS 20.0 package program. Power analysis showed that it was required to include at least 523 MII oocytes per group for a power of 80% at an alpha level of 0.05 in order to detect a difference of 10% in blastocyst

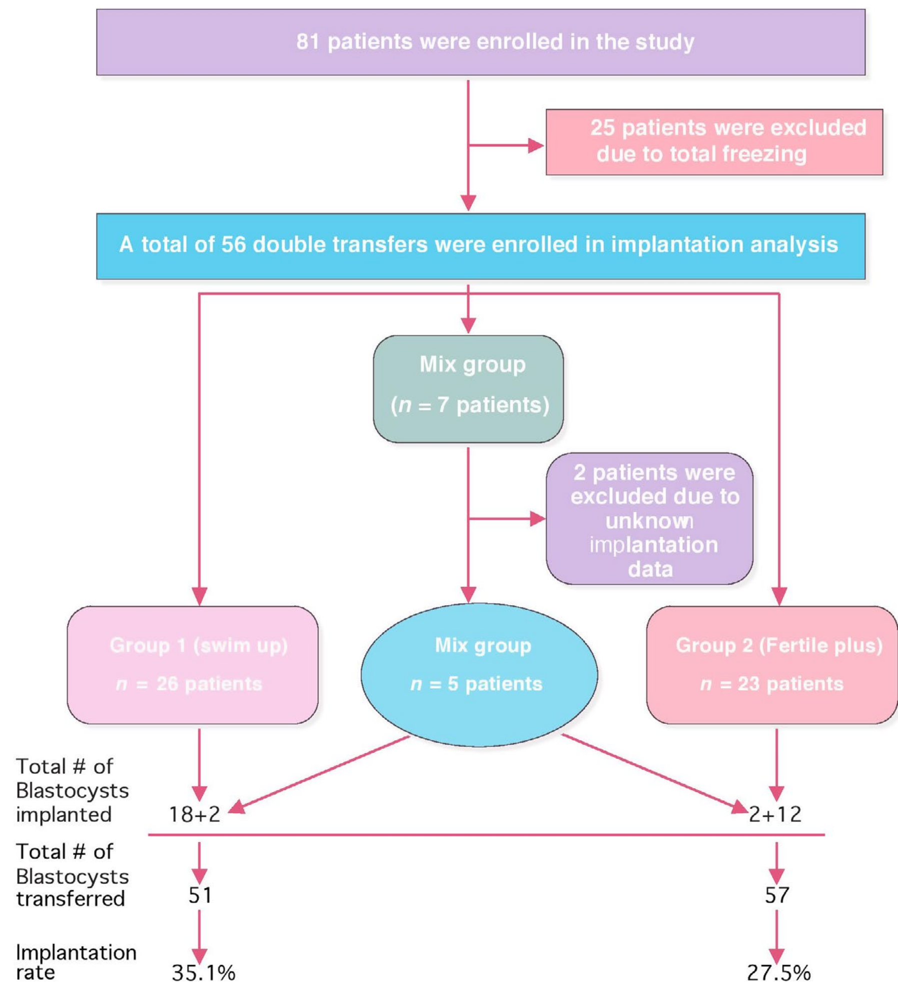


FIGURE 1 Patient enrolment for implantation analysis

TABLE 1 Laboratory outcomes of ICSI cycles using conventional swim up versus Fertile Plus® (including sibling oocytes of 81 patients in both groups)

Variables	Group 1 (swim up; *n* = 81)	Group 2 (Fertile Plus®; *n* = 81)	*p* value
No. of MII oocytes	8.07 ± 4.0	8.15 ± 4.3	.88
No. of fertilized oocytes	6.38 ± 3.4	6.36 ± 3.5	.83
No. of good quality embryos on Day 2	5.53 ± 3.6	5.54 ± 3.4	.99
No. of total blastocysts	3.9 ± 2.8	4.06 ± 2.9	.78
No. of top quality blastocysts[a]	2.73 ± 2.4	2.75 ± 2.3	.87

[a]Blastocysts having a C grade in either ICM and/or TE were excluded from the analysis of top quality blastocysts.

development rate. As a result, a total of 81 patients having a total of 1,314 mature oocytes (including 654 in swim-up group and 660 in Fertile Plus® group) were included in the study. The difference between both groups was compared by Mann–Whitney *U* test for laboratory outcomes such as MII oocytes, fertilised oocytes, good quality day 2 embryos, total blastocyst and top quality blastocysts.

Clinical outcomes were analysed on a total of 56 patients as a subgroup analysis due to the exclusion of 25 patients who did not undergo embryo transfer and had total freezing of embryos. Among these, 26 patients were transferred double blastocysts from swim-up group, 23 patients were transferred double blastocysts from Fertile Plus group and seven patients were transferred double blastocysts including one from each group (shown as mix group in Figure 1). Implantation rates were calculated by dividing total number of blastocysts with known implantation to total number of embryos transferred in both groups, and the results were compared by chi-square test. In addition, clinical pregnancy and live birth rates were compared between groups by using chi-square test. A value of $p < .05$ was considered as statistically significant for all analyses.

3 | RESULTS

Among 81 patients included in the study, aetiologies for infertility were tubal factor in 10, male factor in 21, diminished ovarian reserve in five, endometriosis in two and unexplained in 43 patients. Due to sibling oocyte design, mean ages of females and males in both groups were the same including 29.9 ± 5.4 years old for females and 31.8 ± 3.4 years old for males ($p > .05$). In terms of semen characteristics of the male patients in the study, mean semen volume was found to be 3.2 ± 1.1 ml; mean sperm concentration was $45 \times 10^6 \pm 23 \times 10^6$ million/ml; total motility was 58 ± 21%; and progressive motility was 34 ± 16%.

Laboratory outcomes of both groups including 81 patients are given in Table 1. The groups were found to be comparable in terms of all laboratory outcomes analysed in the study ($p > .05$ for each).

Patient enrolment for implantation analysis is shown in detail in Figure 1. Among 26 double transfers in swim-up group, there were 13 clinical pregnancies including five twin and eight singleton pregnancies; among 23 double transfers in chip group, there were 11 clinical pregnancies including one twin and 10 singleton pregnancies. In the mix group, there were two twin pregnancies (which were included in implantation analysis) and two singletons (which were not included in implantation analysis). Therefore, implantation analysis could be performed on a total of 54 patients whose transferred embryos had a known implantation data (excluding two patients having only one sac in the mix group as shown in Figure 1). Implantation rates were found to be 35.1% and 27.5% in the swim-up versus Fertile Plus® groups respectively. Although there was an increase in the swim-up group in terms of implantation, the difference did not reach a statistical significance ($p = .058$).

Comparison of both groups in terms of clinical outcomes is given in Table 2. Clinical outcomes were compared on a total of 49 patients (including 26 in swim-up group and 23 in Fertile Plus® group); mean age of the women in both groups was 28.8 ± 3.2 versus 31.1 ± 2.6 years respectively ($p > .05$). The differences between groups were not found to be statistically significant in terms of clinical pregnancy, live birth rate and miscarriage rates ($p > .05$ for each).

4 | DISCUSSION

Despite its increased use in clinical assisted reproductive technologies (ART) for sperm sorting, potential contribution of microfluidic-based chips to laboratory and clinical outcomes of ICSI cycles have not been reported yet. This situation has drawn our attention to

TABLE 2 Comparison of the clinical outcomes in both groups

Variables	Group 1 (swim up; *n* = 26 patients)	Group 2 (Fertile Plus®; *n* = 23 patients)	*p* value
Pregnancy rate (*n*/%)	17/65%	14/61%	>.05
Clinical pregnancy rate (*n*/%)	13/50%	11/48%	>.05
Miscarriage rate (*n*/%)	4/15%	3/13%	>.05

conduct a study with these chips which are widely used as a sperm sorting method in our country.

In the current literature, there is only one published study that reports the effects of using microfluidic chips for sperm selection in ICSI cycles compared with conventional swim-up method among cases with unexplained infertility (Yetkinel et al., 2019). The data of this study showed that fertilisation rates were found to be comparable between groups; but, a number of grade 1 embryos were found to be significantly higher in microfluidic group. The authors concluded that the number of surplus embryos was increased in this group leading to a higher rate of embryo freezing. However, this study also lacked many information regarding number of embryos transferred and embryo transfer day which are known to affect laboratory and clinical success significantly.

Our primary aim in this study was to determine whether microfluidic chip-based sperm selection would enhance laboratory outcomes and especially total blastocyst development rates of ICSI patients whose embryos were cultured up to blastocyst stage (days 5 and 6). Therefore, the patients who were initially enrolled in the study but required day 3 transfer due to any embryo developmental problems and/or impaired fertilisation were excluded from the study. We only included patients whose embryos could develop until day 5/6 (either transfer and/or total freezing) since blastocyst development is the most important criteria determining laboratory success in assisted reproduction. Besides, a study on sperm selection should not underestimate that late paternal effects are more visible in blastocyst development rates (Neyer et al., 2015). Our data showed that both groups were comparable in terms of laboratory outcomes and indicated no positive add-on effect of sperm selection by using chip. Also, sibling oocyte design of the study helped to make a more reliable comparison between groups by eliminating female-induced bias that has a great potential to change the outcomes dramatically.

Clinical pregnancy, implantation and live birth rates were the secondary outcomes of the study; our results also did not show any advantage of the chip over conventional swim up in terms of these parameters. Although they were found to be slightly higher in swim-up group, the differences did not reach statistical significance. This was thought to be due to higher maternal age in Fertile group. The studies regarding the use of microfluidic chips for sperm sorting supported that these chips were able to sort spermatozoa with higher DNA integrity (Quinn et al., 2018; Schulte et al., 2007); these devices were introduced to ART market with the claim that their use might be beneficial for decreasing miscarriage rates which were reported to be affected by higher sperm DNA fragmentation (Carlini et al., 2017; Kumar et al., 2012). The results of our study showed no significant difference in miscarriage rates between both groups and did not support any advantage of chip over conventional sorting methods in terms of this outcome.

Our study also has some limitations. Firstly, clinical outcomes were evaluated on a limited number of patients in the study since some of them did not undergo embryo transfer due to various factors. In addition, we chose blastocysts for transfer depending on the final morphological assessment; although we randomly assigned patients to choose both blastocysts for transfer from the same group, it was impossible in some cases where good quality blastocysts were not developed within the same group. We could include five more patients from the mix group in implantation analysis to minimise exclusion of cases since implantation analysis is based on the number of embryos implanted. However, since the other clinical outcomes such as CPR and LBR are calculated per number of patients in the groups, the patients in both study (Fertile Plus®) and control groups (swim up) remained limited; this was the major limitation for making a powerful comparison in this aspect.

In addition to these, another limitation was the limited inclusion criteria in the study. Although we excluded patients having any acute and/or chronic diseases in the beginning of study, we did not get additional information in terms of their lifestyles. Besides, we could not exclude any patients who might have genetic abnormalities in their gametes and/or embryos. Genetic screening of the embryos would be beneficial to provide validation to our outcomes; but, none of the patients wanted to undergo these genetic tests due to financial reasons.

In conclusion, results of this study have shown that sorting spermatozoa through Fertile Plus® does not improve laboratory outcomes significantly. It also does not have a positive add-on effect in terms of clinical outcomes; but, more data are needed through prospective, randomised controlled trials including larger samples in order to make a more comprehensive analysis.

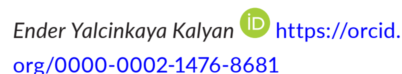
ACKNOWLEDGEMENTS

None declared.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID


Ender Yalcinkaya Kalyan https://orcid.org/0000-0002-1476-8681

REFERENCES

Avalos-Duran, G., Canedo-Del Angel, A. M., Rivero-Murillo, J., Zambrano-Guerrero, J. E., Carballo-Mondragon, E., & Checa-Vizcaino, M. A. (2018). Physiological ICSI (PICSI) vs. conventional ICSI in couples with male factor: A systematic review. *JBRA Assisted Reproduction*, *22*(2), 139–147.

Boulet, S. L., Mehta, A., Kissin, D. M., Warner, L., Kawwass, J. F., & Jamieson, D. J. (2015). Trends in use of and reproductive outcomes associated with intracytoplasmic sperm injection. *JAMA*, *313*(3), 255–263. https://doi.org/10.1001/jama.2014.17985

Carlini, T., Paoli, D., Pelloni, M., Faja, F., Dal Lago, A., Lombardo, F., … Gandini, L. (2017). Sperm DNA fragmentation in Italian couples with recurrent pregnancy loss. *Reproductive BioMedicine Online*, *34*, 58–65. https://doi.org/10.1016/j.rbmo.2016.09.014

Chinnasamy, T., Behr, B., & Demirci, U. (2016). Microfluidic sperm sorting device for selection of functional human sperm for IUI application. *Fertility and Sterility*, *105*(2), e17–e18. https://doi.org/10.1016/j.fertnstert.2015.12.063

Dirican, E. K., Ozgun, O. D., Akarsu, S., Akin, K. O., Ercan, O., Ugurlu, M., … Unsal, A. (2008). Clinical outcome of magnetic activated cell sorting of non-apoptotic spermatozoa before density gradient centrifugation for assisted reproduction. *Journal of Assisted Reproduction and Genetics*, *25*(8), 375–381. https://doi.org/10.1007/s10815-008-9250-1

Ergin, E. G., Caliskan, E., Yalcinkaya, E., Oztel, Z., Cokelez, K., Ozay, A., & Ozornek, H. M. (2014). Frequency of embryo multinucleation detected by time-lapse system and its impact on pregnancy outcome. *Fertility and Sterility*, *102*(4), 1029–1033.

Gardner, D. K., & Schoolcraft, W. B. (1999). Culture and transfer of human blastocysts. *Current Opinion in Obstetrics and Gynaecology*, *11*(3), 307–311. https://doi.org/10.1097/00001703-199906000-00013

Kim, H. J., Yoon, H. J., Jang, J. M., Oh, H. S., Lee, Y. J., Lee, W. D., … Lim, J. H. (2014). Comparison between intracytoplasmic sperm injection and intracytoplasmic morphologically selected sperm injection in oligo-astheno-teratozoospermia patients. *Clinical and Experimental Reproductive Medicine*, *41*(1), 9–14. https://doi.org/10.5653/cerm.2014.41.1.9

Kumar, K., Deka, D., Singh, A., Mitra, D. K., Vanitha, B. R., & Dada, R. (2012). Predictive value of DNA integrity analysis in idiopathic recurrent pregnancy loss following spontaneous conception. *Journal of Assisted Reproduction and Genetics*, *29*, 861–867. https://doi.org/10.1007/s10815-012-9801-3

Neyer, A., Zintz, M., Stecher, A., Bach, M., Wirleitner, B., Zech, N. H., & Vanderzwalmen, P. (2015). The impact of paternal factors on cleavage stage and blastocyst development analyzed by time-lapse imaging—A retrospective observational study. *Journal of Assisted Reproduction and Genetics*, *32*(11), 1607–1614. https://doi.org/10.1007/s10815-015-0558-3

Perez-Cerezales, S., Laguna-Barraza, R., de Castro, A. C., Sanchez-Calabuig, M. J., Cano-Oliva, E., de Castro-Pita, F. J., … Gutierrez-Adan, A. (2018). Sperm selection by thermotaxis improves ICSI outcome in mice. *Scientific Reports*, *8*(1), 2902. https://doi.org/10.1038/s41598-018-21335-8

Quinn, M. M., Jalalian, L., Ribeiro, S., Ona, K., Demirci, U., Cedars, M. I., & Rosen, M. P. (2018). Microfluidic sorting selects sperm for clinical use with reduced DNA damage compared to density gradient centrifugation with swim-up in split semen samples. *Human Reproduction*, *33*, 1388–1393.

Rosenwaks, Z., & Pereira, N. (2017). The pioneering of intracytoplasmic sperm injection – Historical perspectives. *Reproduction*, *154*(6), F71–F77. https://doi.org/10.1530/REP-17-0308

Samuel, R., Feng, H., Jafek, A., Despain, D., Jenkins, T., & Gale, B. (2018). Microfluidic-based sperm sorting & analysis for treatment of male infertility. *Translational Andrology and Urology*, *7*(Suppl 3), S336–S347.

Schulte, R. T., Chung, Y. K., Ohl, D. A., Takayama, S., & Smith, G. D. (2007). Microfluidic sperm sorting device provides a novel method for selecting motile sperm with higher DNA integrity. *Fertility and Sterility*, *88*(Supplement 1), S76. https://doi.org/10.1016/j.fertnstert.2007.07.254

Stimpfel, M., Verdenik, I., Zorn, B., & Virant-Klun, I. (2018). Magnetic-activated cell sorting of non-apoptotic spermatozoa improves the quality of embryos according to female age: A prospective sibling oocyte study. *Journal of Assisted Reproduction and Genetics*, *35*(9), 1665–1674. https://doi.org/10.1007/s10815-018-1242-1

Teixeira, D. M., Barbosa, M. A., Ferriani, R. A., Navarro, P. A., Raine-Fenning, N., Nastri, C. O., & Martins, W. P. (2013). Regular (ICSI) versus ultra-high magnification (IMSI) sperm selection for assisted reproduction. *Cochrane Database of Systematic Reviews*, (7), CD010167. https://doi.org/10.1002/14651858.CD010167.pub2

Worrilow, K. C., Eid, S., Woodhouse, D., Perloe, M., Smith, S., Witmyer, J., … Lieberman, J. (2013). Use of hyaluronan in the selection of sperm for intracytoplasmic sperm injection (ICSI): Significant improvement in clinical outcomes – Multicenter, double-blinded and randomized control trial. *Human Reproduction*, *28*(2), 306–314.

Yetkinel, S., Kilicdag, E. B., Aytac, P. C., Haydardedeoğlu, B., Simsek, E., & Cok, T. (2019). Effects of the microfluidic chip technique in sperm selection for intracytoplasmic sperm injection for unexplained infertility: A prospective, randomized controlled trial. *Journal of Assisted Reproduction and Genetics*, *36*(3), 403–409. https://doi.org/10.1007/s10815-018-1375-2

How to cite this article: Yalcinkaya Kalyan E, Can Celik S, Okan O, Akdeniz G, Karabulut S, Caliskan E. Does a microfluidic chip for sperm sorting have a positive add-on effect on laboratory and clinical outcomes of intracytoplasmic sperm injection cycles? A sibling oocyte study. *Andrologia*. 2019;51:e13403. https://doi.org/10.1111/and.13403