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Testicular function and fertility outcomes in males with CF: A multi center retrospective study of men with congenital bilateral absence of the vas deferens based on CFTR mutation status

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ABSTRACT

Background: Modern cystic fibrosis (CF) treatments, particularly CFTR modulators, have allowed males with CF (MwCF) to live longer, healthier lives and pursue parenthood. Approximately 98% of MwCF have congenital bilateral absence of the vas deferens (CBAVD). While research shows MwCF experience spermatogenic dysfunction alongside obstructive azoospermia, understanding male reproductive health in MwCF remains limited. This study retrospectively examines testicular function and intracytoplasmic sperm injection outcomes of the partners of males with CBAVD, stratified by CF mutation status (CF, CF carriers, no known mutation).
Subjects and Methods: This multicenter, retrospective study assessed sperm retrieval outcomes and testicular function in males with CBAVD. Participants were categorized into three groups: MwCF (Group 1), CFTR gene mutation carriers (CFTR carriers, Group 2), and CBAVD males without CFTR mutations (Group 3). We collected data on genetic testing, testicular hormone levels (FSH, LH, total testosterone), sperm retrieval methods, and reproductive outcomes. Statistical analysis was used to assess intergroup differences.
Results: Thirty subjects were included (Group 1: 14, Group 2: 11, Group 3: 5). No significant differences in demographic, anthropometric, or reproductive characteristics were found across groups. Hormone levels (LH, FSH, and testosterone) were similar among groups. In Group 1, 42 % had elevated FSH levels. The prevalence of hypogonadism was 16.7 % in Group 1. Group 3 had a significantly lower fertilization rate ($p < 0.01$), but no differences were found in blastocyst formation, pregnancy, miscarriage, or live birth rates.
Conclusions: Our data support the presence of primary spermatogenic dysfunction in some MwCF. However, reproductive outcomes were similar across all groups.

Introduction

The advent of novel therapies for cystic fibrosis (CF) has significantly extended the life expectancy for CF subjects over the last several years. This monumental shift in outcomes has allowed for a focus on quality-of-life issues for these individuals [1]. Intracytoplasmic sperm injection (ICSI) is an advanced reproductive technology used to assist couples with infertility by enabling the fertilization of an oocyte in a laboratory setting by directly injecting a sperm into an oocyte. Ninety-eight percent of males with CF (MwCF) have congenital bilateral absence of the vas deferens (CBAVD), defined as the absence the vas deferens bilaterally and typically absence or anomalies of the seminal vesicles and epididymes. As a result, MwCF are almost uniformly azoospermic due to obstruction to sperm flow. To overcome this, surgical sperm retrieval is necessary, where sperm is extracted directly from the testes or epididymis. The retrieved sperm is then used in intracytoplasmic sperm injection (ICSI), a form of *in vitro* fertilization (IVF) [2] where a single sperm is injected into an egg for fertilization. If successful, the fertilized oocyte can be cultured and then transferred into the woman's uterus [3]. Given the need for large multi-institutional studies to determine how these subjects fare with assisted reproduction, there remains gaps in knowledge which limits the reproductive urologist's ability to counsel

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these people. Additionally, most of the published data is from prior to widespread use CFTR modulators, which have significantly improved other CF parameters, such as pulmonary and endocrine function. Given this, it is reasonable to question whether testicular function and reproductive outcomes might also improve.

Limited data exists regarding the clinical impact of CF on sperm quality and function which is key to understanding ICSI outcomes for this population. There is evidence to suggest that their outcomes are distinguishable from individuals with obstructive azoospermia due to other etiologies (i.e. vasectomy) where systemic illness is absent. McBride et al compared ICSI outcomes in males with CBAVD without CF to males with CBAVD with CF in the pre- CFTR modulators era. The CF group had lower concentrations of sperm retrieved and worse fertilization rate with ICSI [4]. Lu et al retrospectively reviewed 1414 ICSI cycles performed in males with and without a *CFTR* mutation and noted a higher miscarriage rate in those with a *CFTR* mutation compared to males without suggesting a sperm quality impairment [5]. Multiple factors likely contribute to worse ICSI outcomes in this population and CF-specific disease factors may predict which males are likely to fare better or worse as is true for many males with chronic illness. Interestingly, Sapru and colleagues published a series of 67 MwCF undergoing IVF/ICSI at a single center and their reproductive outcomes were similar to healthy men [6].

The mechanism behind reduced ICSI success rates demonstrated in some studies in MwCF is poorly understood and likely multifactorial. Sperm CFTR expression has been demonstrated to be higher in healthy fertile males compared to males who had not caused a pregnancy [7]. The CFTR gene is known to be expressed in mature spermatozoa and its expression impacts capacitation, morphology and motility of sperm [8,9]. Given the knowledge that *CFTR* expression is tied to male fertility potential, we aimed to examine reproductive outcomes and hormonal status in males with CBAVD based on *CFTR* mutation status. Based on the limited existing data, we hypothesized that MwCF would have worse reproductive outcomes than CF carriers and CBAVD no-mutation males. Similarly, we hypothesized that the prevalence of testicular dysfunction as measured by testosterone, FSH, and LH would be higher in MwCF.

Subjects and methods

Experimental protocol

This multicenter, retrospective study was conducted across two institutions in males with CBAVD undergoing sperm retrieval. The study specifically identified three groups of males with CBAVD: MwCF, carriers of *CFTR* gene mutations (*CFTR* carriers), and males without *CFTR* gene mutations. The primary objective was to assess testicular function, sperm retrieval outcomes, and ICSI success rates (fertilization, pregnancy and live birth rate) among these three groups. We performed an intergroup comparison to evaluate differences between the groups.

We compared sperm retrieval outcomes, ICSI outcomes and gonadal function in males with CBAVD among MwCF, males with CFTR mutations without CF and males without CFTR mutations.

Study population

The population in this study consisted of male individuals diagnosed with CBAVD who underwent surgical sperm retrieval followed by ICSI at two participating institutions. CBAVD was confirmed through based on physical exam by an experienced reproductive urologist and semen analysis parameters when available. Additionally, all subjects underwent genetic testing to determine CFTR mutation status as recommended by American Urological Guidelines [10], which was essential for the classification of participants. Mutations were assessed by sequencing the gene using Sanger sequencing, a highly accurate method that allows for the identification of both known and novel mutations. This technique involves amplifying the CFTR gene, followed by direct sequencing of the amplified regions to detect potential mutations or variants.

Males were referred to the two participating institutions for fertility treatment, primarily due to issues related to male infertility associated with CBAVD. The referral period for participants included the time span ranging from January 2010 to December 2024. This recruitment was conducted in collaboration with urologists and fertility specialists at these centers, with males being diagnosed with CBAVD based on a combination of clinical signs (e.g., absence of the vas deferens) and genetic testing confirming CFTR mutations or the absence thereof.

Inclusion criteria for the study were as follows: males aged 18 years or older with a clinical diagnosis of CBAVD, who underwent sperm retrieval and subsequent ICSI. Exclusion criteria included individuals with other known causes of infertility unrelated to CBAVD, such as obstructive azoospermia from other etiologies, or those with conditions known to cause hypogonadism or testicular dysfunction. We excluded males with non-CF severe systemic illnesses.

We categorized the study participants into three distinct groups based on their genetic diagnosis: those with CF (**Group 1**), CFTR carriers (**Group 2**), and those with no detectable CFTR gene mutations (**Group 3**). This classification allowed for a comparison of reproductive outcomes and hormonal status across these genetically distinct subpopulations.

Data collection

We collected clinical and demographic data for both the male and female partner, including age, race, lifestyle habits (i.e., alcohol intake, cigarette smoke), body mass index (BMI), medical history, presence of other congenital abnormalities, and details of previous fertility evaluations, when available. We recorded data on genetic testing (i.e., *CFTR* gene mutation), FEV1 around time of sperm retrieval, and use of CFTR modulators. We also collected information on testicular function, including serum levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone (TT). The definition of hypogonadism was TT $<$ 300 ng/dL for the purposes of this study based on the American Urological Association Testosterone Deficiency Guidelines [11]. We assessed the percentage of males with FSH values $>$ 7.6 IU/L [12] as a marker of primary testicular failure. We systematically recorded sperm retrieval outcomes, including the method of retrieval (e.g., percutaneous epididymal sperm aspiration [PESA], microsurgical epididymal sperm aspiration [MESA], testicular sperm extraction [TESE] or micro-TESE), number of sperm retrieved post-wash, and sperm motility. ICSI-related outcomes were captured when available, including the stimulation protocol used, the number of follicles and of mature/immature oocytes retrieved, rates of fertilization, embryo quality, clinical pregnancy, gestational week at delivery, live birth and infant birth weight.

Hormone measurements

Blood samples were obtained in the morning, between 8:00 and 9:00 am, following an overnight fast. The serum concentrations of LH, FSH, and TT were assessed using an electrochemiluminescence immunoassay (Cobas 6000, Hitachi-Roche, Roche Diagnostics, Indianapolis, IN, USA). The reference intervals for the assays were as follows: LH: 1.14–8.75 mIU/mL, FSH: 0.95–11.95 mIU/mL, and TT: 300–877 ng/dL.

Statistical analysis

Continuous data are shown as mean ± standard deviation (SD) for non-skewed variables and median with interquartile range (IQR) for non-normally distributed variables. We evaluated data distribution using the Shapiro-Wilk test. Dichotomous data are shown as numbers (percentages). We calculated fertilization rates considering the number of embryo fertilized (proven by the presence of pronuclei [pns]) normalized for the total number of mature oocytes injected. Chemical

pregnancy rates (positive human chorionic gonadotropin blood test), miscarriage and live birth rates were calculated for number of embryo transfers (ET). We assessed between group differences using the One-way Analysis of Variance (ANOVA) or the Kruskal-Wallis test, for normally or non-normally distributed variables respectively, as appropriate. We used repeated $\chi 2$ tests to compare categorical variables. We performed statistical analysis using MedCalc Software Ltd. (Ostend, Belgium), version 19.6–64-bit. A p-value less than 0.05 was considered statistically significant.

Results

Descriptive analysis

A total of 30 males met the eligibility criteria. 14 males were assigned to Group 1, 11 to Group 2, and 5 to Group 3 based on their CFTR mutation status as described above. The demographic and anthropometric characteristics of the enrolled males and their partners are presented in Table 1 and Table 2, respectively. No significant differences were observed among the subjects in terms of age ($p = 0.29$), BMI ($p = 0.31$), race ($p = 0.06$), ethnicity ($p = 0.12$), smoking ($p = 0.95$), or drinking ($p = 0.70$) habits. Similarly, their female partners showed comparable characteristics in terms of age ($p = 0.09$), BMI ($p = 0.11$), race ($p = 0.08$), and ethnicity ($p = 0.12$). Reproductive characteristics were also similar across groups, with no intergroup differences found in statistical analysis. No significant differences in the distribution of infertility diagnoses among the female partner were observed ($p = 0.65$). Additionally, levels of anti-Müllerian hormone (AMH) were similar among the groups ($p = 0.40$), as were the basal antral follicle counts ($p = 0.87$).

FEV1 values were available for 6 MwCF (42.9 %), with a median (interquartile range) of 3.5L (2.1–4.2) (normal values: 4.5–5.5 L). Genetic testing results were available for 5 Group 1 males and all Group 2 and Group 3 males. Finally, 7/14 Group 1 males were receiving CFTR modulators (Ivacaftor or Elexacaftor/Tezacaftor/Ivacaftor).

Table 1
Demographic and anthropometric characteristics of the males included in the study.

		Group 1 (n = 14)	Group 2 (n = 11)	Group 3 (n = 5)	p-values
Male race	Asian	0 (0.0 %)	0 (0.0 %)	1 (20.0 %)	0.06
	Black or African American	0 (0.0 %)	2 (18.2 %)	0 (0.0 %)	
	White	13 (92.9 %)	9 (81.8 %)	3 (60.0 %)	
	Other	0 (0.0 %)	0 (0.0 %)	1 (20.0 %)	
	Unknown	1 (7.1 %)	0 (0.0 %)	0 (0.0 %)	
Ethnicity	Not Hispanic or Latino	14 (100.0 %)	11 (100.0 %)	5 (100.0 %)	0.12
Smoking	Yes	3 (21.4 %)	3 (27.3 %)	1 (20.0 %)	0.95
	No	10 (71.4 %)	7 (63.6 %)	4 (80.0 %)	
	Unknown	1 (7.1 %)	1 (9.1 %)	0 (0.0 %)	
Alcohol intake	≤6 drinks/ week	11 (78.6 %)	10 (90.9 %)	4 (80.0 %)	0.70
	≤6 drinks/ week	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
	Unknown	3 (21.4 %)	1 (9.1 %)	1 (20.0 %)	
Age (years)		33.50 ± 3.90	35.55 ± 3.67	35.80 ± 2.17	0.29
Body mass index (Kg/m^2)		23.71 (23.06 – 27.82)	26.87 (25.07 – 28.17)	25.24 (23.09 – 27.25)	0.31

Group 1 includes males diagnosed with cystic fibrosis; Group 2 includes carriers of the *CFTR* gene mutation; Group 3 includes males with congenital bilateral absence of vas deferens (CBAVD) with no evidence of *CFTR* gene mutation.
Continuous data were shown as the median [interquartile range (IQR)] for non-normally distributed continuous variables and as the mean ± standard deviation (SD) for normally distributed variables. The distribution of the data was assessed using the Shapiro-Wilk test. The Mann-Whitney *U* test was used for non-normally distributed variables, while the Student's *t*-test was applied to normally distributed variables to compare between-group differences. Dichotomous variables were shown as number (percentages). Between-group differences in dichotomous variables were assessed using the $\chi 2$ test. All percentages have been rounded to one decimal place. A p-value of < 0.05 was considered statistically significant.

Table 2
Demographic and anthropometric characteristics of the female partners of the males included in the study.

		Group 1 (n = 14)	Group 2 (n = 11)	Group 3 (n = 5)	p-values
Female race	Asian	2 (14.3 %)	0 (0.0 %)	2 (40.0 %)	0.08
	Black or African American	0 (0.0 %)	2 (18.2 %)	1 (20.0 %)	
	White	9 (64.3 %)	9 (81.8 %)	2 (40.0 %)	
	Unknown	3 (21.4 %)	0 (0.0 %)	0 (0.0 %)	
Female ethnicity	Not Hispanic or Latino	14 (100.0 %)	11 (100.0 %)	5 (100.0 %)	0.12
Infertility	No	13 (92.9 %)	9 (81.8 %)	4 (80.0 %)	0.65
	Diminished ovarian reserve	0 (0.0 %)	1 (9.1 %)	0 (0.0 %)	
	Ovulatory dysfunction	1 (7.1 %)	1 (9.1 %)	1 (20.0 %)	
Antral follicle count (n)		22.25 ± 9.77	22.73 ± 16.33	19.20 ± 8.76	0.87
Age (years)		31.64 ± 4.11	34.82 ± 3.28	34.0 ± 1.58	0.09
Body mass index (Kg/m^2)		25.61 (23.20 – 30.27)	24.03 (21.91 – 31.50)	20.89 (20.49 – 22.16)	0.11
AMH (ng/mL)		3.80 (2.53 – 5.03)	3.10 (1.55 – 3.75)	2.90 (2.23 – 4.18)	0.40

AMH, Anti-Müllerian hormone.
Group 1 includes males diagnosed with cystic fibrosis; Group 2 includes carriers of the *CFTR* gene mutation; Group 3 includes males with congenital bilateral absence of vas deferens (CBAVD) with no evidence of *CFTR* gene mutation.
Continuous data were shown as the median [interquartile range (IQR)] for non-normally distributed continuous variables and as the mean ± standard deviation (SD) for normally distributed variables. The distribution of the data was assessed using the Shapiro-Wilk test. The Mann-Whitney *U* test was used for non-normally distributed variables, while the Student's *t*-test was applied to normally distributed variables to compare between-group differences. Dichotomous variables were shown as number (percentages). Between-group differences in dichotomous variables were assesses using the $\chi 2$ test. All percentages have been rounded to one decimal place. A p-value of < 0.05 was considered statistically significant.

Testicular function

Hormone values were available for 12 (87.7 %) MwCF, 1 (9.1 %) carrier, and 1 (20.0 %) CBAVD patient. No intergroup differences were observed for LH ($p = 0.35$), FSH ($p = 0.19$) and TT ($p = 0.69$). Notably, FSH levels > 7.6 IU/L were observed in 5 (41.7 %) males in Group 1. Two males (16.7 %) had hypogonadism, with an apparent unexplained etiology.

Regarding sperm retrieval, no significant differences were observed between groups in terms of the distribution of cryopreserved (retrieved prior to egg retrieval and cryopreserved) vs. fresh (retrieved same day as egg retrieval) sperm ($p = 0.11$) or the surgical procedure used ($p =$

0.31). No intergroup differences were found in the frequency of motile sperm retrieved (p = 0.95).

Reproductive outcomes

All males underwent ICSI, which unexpectedly resulted in a significantly lower fertilization rate in Group 3 compared to the other groups (p < 0.01). No differences were observed in the blastocyst rate (p = 0.98) across the three groups, nor in other pregnancy-related outcomes, including pregnancy rate (p = 0.59), miscarriage rate (p = 0.79), and live birth rate (p = 0.58). The groups were also similar in terms of gestational week at delivery (p = 0.61) and birthweight (p = 0.13) (Table 3).

Discussion

The advent of CFTR modulators has extended the life expectancy of MwCF, leading to an imperative to understand quality-of-life issue [1]. Options for reproduction for MwCF is an important topic for these subjects as they live well into adulthood. The majority of MwCF can safely undergo surgical sperm retrieval with assisted reproduction however our understanding of their outcomes is limited. The contribution of CFTR to sperm function has been well studied [7]. Despite this, there are very few studies examining reproductive outcomes for MwCF and none completed in the post- CFTR modulators era. Several barriers exist to gathering this data: small populations served at individual centers and a need for multi-institutional studies, lack of standardization of sperm retrieval outcomes, and the inherent need for female partner data to draw meaningful reproductive outcomes.

Table 3
Pregnancy-related outcomes.

		Group 1 (n = 14)	Group 2 (n = 11)	Group 3 (n = 5)	p-values
Fertilization rate (%)		58.6 ± 20.2	75.2 ± 14.5	36.6 ± 38.0	**0.012**
Blastocyst rate (%)		49.1 ± 36.1	46.2 ± 30.9	49.2 ± 48.3	0.978
Positive hCG*	Yes	7 (63.6 %)	9 (81.8 %)	3 (75.0 %)	0.6272
	No	4 (26.4 %)	2 (18.2 %)	1 (25.0 %)	
Clinical pregnancy rate*	Yes	5 (45.5 %)	7 (63.6 %)	3 (75.0 %)	0.5929
	No	2 (18.2 %)	2 (18.2 %)	0 (0.0 %)	
Miscarriage rate*	Yes	1 (9.1 %)	1 (9.1 %)	0 (0.0 %)	0.7940
	No	6 (54.1 %)	8 (72.7 %)	3 (75.0 %)	
Live birth rate*	Yes	4 (36.4 %)	6 (54.5 %)	3 (75.0 %)	0.5836
	No	0 (0.0 %)	1 (9.1 %)	0 (0.0 %)	
Multiple pregnancies**	No	4 (100.0 %)	4 (66.7 %)	2 (66.7 %)	0.5890
	Twins	0 (0.0 %)	1 (14.3 %)	0 (0.0 %)	
	Triple	0 (0.0 %)	1 (14.3 %)	1 (33.3 %)	
Gestational week at delivery		36.8 ± 2.6	38.6 ± 2.1	38.0 ± 2.7	0.6130
Birthweight (g)		3046.5 ± 924.8	3106.7 ± 247.3	3473.0 ± 260.2	0.1250

hCG, human chorionic gonadotropin
*Calculated per embryo transfer (n = 11 for Group 1, n = 11 for Group 2, n = 4 for Group 3); **calculated per live birth (n = 4 for Group 1, n = 6 for Group 2, n = 3 for Group 3).
Group 1 includes males diagnosed with cystic fibrosis; Group 2 includes carriers of the *CFTR* gene mutation; Group 3 includes males with congenital bilateral absence of vas deferens (CBAVD) with no evidence of *CFTR* gene mutation.
Continuous data were shown as the median [interquartile range (IQR)] for non-normally distributed continuous variables and as the mean ± standard deviation (SD) for normally distributed variables. The distribution of the data was assessed using the Shapiro-Wilk test. The Mann-Whitney *U* test was used for non-normally distributed variables, while the Student's *t*-test was applied to normally distributed variables to compare between-group differences. Dichotomous variables were shown as number (percentages). Between-group differences in dichotomous variables were assessed using the $\chi 2$ test. All percentages have been rounded to one decimal place. A p-value of < 0.05 was considered statistically significant.

This study is the first to compare multiple clinical parameters and reproductive outcomes in males with CBAVD by *CFTR* mutation status in the post CFTR modulators era. The data revealed higher fertilization rates in Group 2 (CF carriers) however all other ICSI outcomes were similar across all groups which is reassuring. Interestingly, elevated FSH levels were observed in 41.7 % of Group1 males, suggesting testicular dysfunction in a significant number of MwCF in this study group.

A growing body of literature has examined hypogonadism and infertility in MwCF, particularly with regard to the role of CFTR mutations in reproductive health [4–9]. A recent retrospective study on 69 MwCF demonstrated the presence of low T in roughly a quarter of males [13]. Studies have shown that CF-related male infertility, often characterized by CBAVD, results from defective CFTR function in the epididymis, leading to obstructive azoospermia [14]. The introduction of CFTR modulators has provided significant improvements in the overall health and life expectancy of MwCF [1], but it is still unclear how these treatments may impact reproductive health. Notably, while previous studies have shown that a majority of MwCF can successfully undergo sperm retrieval with ICSI [3], our understanding of long-term outcomes and the impact of CFTR modulators on male fertility is still limited. This is particularly true in the context of sperm retrieval outcomes, where variability in protocols across centers and a lack of standardized reporting, including how to measure sperm quantity and quality in the setting of surgically retrieved sperm, pose significant challenges to drawing generalizable conclusions.

The importance of this research extends beyond clinical interest and is highly relevant for both CF providers and fertility specialists. For clinicians, understanding the potential for testicular dysfunction and its impact on fertility outcomes in MwCF is essential for providing comprehensive care, counseling patients and families on reproductive options, and making informed decisions about CFTR modulator therapies. If larger studies reproduce our findings, it may demonstrate a clinical need for screening for hypogonadism in adult CF males. For fertility specialists, awareness of the unique challenges faced by males with CF, including potential hormonal imbalances and varied ICSI outcomes compared to non-CF males, is critical for pre-operative planning and setting patient expectations. Moreover, with CFTR modulators altering the disease state substantially, it is reasonable to consider that they might impact testicular health as well. It is crucial for both CF specialists and fertility clinics to remain vigilant in monitoring the reproductive health of these patients.

This study has several limitations. Primarily, our study population is small and complete data was not available for all males. In particular, hormone data was scarcely available for non-CF males which is expected as these males are presumably less likely to have testicular dysfunction. The unavailability of genetic testing data for some individuals with CF was due to variability in the medical records across institutions. This limitation may affect the completeness of the data for certain participants. Surgical approaches varied by center which is expected given lack of standardization of surgical approaches in CBAVD males. Additionally, when testicular tissue and epididymal aspirate samples are processed by andrologists or embryologists, there is no standardized process for reporting unlike a standard semen analysis for which the WHO has a dedicated manual. As a result, we were unable to report on sperm retrieval outcomes specifically in this dataset. Finally, the results of the subgroup analyses herein reported must be taken with care since these are limited by the low sample size. There is a need for a larger multi-institutional study with standardized reporting of sperm retrieval

outcomes. Prospective collection would allow for this as well as complete hormone data. The need to understand testicular function and reproductive outcomes in MwCF is paramount and our study is the first to explore this among CBAVD males by CFTR mutation status in the CFTR modulators era.

In conclusion, the findings from this study, although limited by sample size and variability in data, underscore the importance of continuing research in this area. Expanding to multi-center large retrospective and prospective studies with standardized protocols for sperm retrieval and reporting, along with guidelines for hormonal evaluation, are imperative to better understand the long-term reproductive outcomes for MwCF. This knowledge will not only aid clinicians in providing targeted care but also help empower patients and families to make informed decisions about their reproductive futures. Finally, more mechanistic studies will need to be completed to understand the role of CFTR in sperm function and subsequent embryo development.

CRediT authorship contribution statement

Rossella Cannarella: Writing – original draft, Validation, Methodology, Formal analysis, Conceptualization. **Danielle Velez Leitner:** Writing – original draft, Investigation, Data curation. **Marissa Weiss:** Writing – original draft, Investigation, Data curation. **Sarah C. Vij:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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