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Globozoospermia: A Case Report and Systematic Review of Literature

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Purpose: Globozoospermia is a genetic syndrome characterized by the presence of round-headed spermatozoa and infertility due to the inability of these spermatozoa to fertilize the oocyte. In this article, we present the clinical case of a young globozoospermic patient with a new, not yet described mutation of the *DPY19L2* gene. We also performed a systematic review of the literature on gene mutations, the outcome of assisted reproductive techniques, and the risk of transmission of abnormalities to the offspring in patients with globozoospermia and made recommendations to offer a more appropriate clinical management of these patients.

Materials and Methods: We performed a systematic search in the PubMed, Google Scholar, and Scopus databases from their inception to December 2021. The search strategy included the combination of the following Medical Subjects Headings (MeSH) terms and keywords: "globozoospermia", "round-headed spermatozoa", "round head spermatozoa", "intracytoplasmic sperm injection", "ICSI", "offspring", "child health", "assisted reproductive technique outcome". All the eligible studies were selected following the PECOS (Population, Exposure, Comparison/Comparator, Outcomes, Study design) model. The quality of included studies was assessed by applying the "Cambridge Quality Checklists".

Results: The main genes involved in the pathogenesis of globozoospermia are *DPY19L2*, *SPATA16*, *PICK1*, *GGN*, *SPACA1*, *ZPBP*, *CCDC62*, and *CCNB3* genes. Other genes could also play a role. These include *C2CD6*, *C7orf61*, *CCIN*, *DNH17*, *DNH6*, *PIWIL4*, and *CHPT1*. Globozoospermic patients should undergo ART to achieve fertility. In particular, intracytoplasmic sperm injection with assisted oocyte activation or intracytoplasmic morphologically-selected sperm injection appears to be associated with a higher success rate. Patients with globozoospermia should also be evaluated for the high rate of sperm aneuploidy which appears to influence the success rate of ART but does not appear to be associated with an increased risk of transmission of genetic abnormalities to offspring.

Conclusions: This systematic review summarizes the evidence on the gene panel to be evaluated, ICSI outcomes, and the health of the offspring in patients with globozoospermia. Evidence-based recommendations on the management of patients with globozoospermia are provided.

Keywords: Assisted reproductive techniques; Globozoospermia; Intracytoplasmic sperm injection; Round-headed spermatozoa

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INTRODUCTION

Infertility is an extremely common condition affecting about 15% of couples worldwide, with a male factor prevalence of 50%. Although great progress has been made in identifying the causes of male infertility, even today a large proportion of these patients do not receive an etiological diagnosis and are diagnosed having idiopathic infertility [1].

Genetic abnormalities seem to play an important role in the pathogenesis of male infertility, accounting for about 15% of the cases. However, likely unidentified genetic causes may also occur in about 40% of patients with infertility, as more than 2,000 genes are involved in spermatogenesis, and their variations may be responsible for quantitative and qualitative defects in spermatogenesis [2].

In the last decade, next-generation sequencing (NGS) has allowed the identification of new genetic targets linked to male infertility [3]. A recent systematic review of the literature, compiling evidence from 1,523 articles analyzing monogenic causes of male infertility and abnormalities of the genitourinary system, concluded that currently about 120 genes are moderately, strongly, or definitively related to 104 infertility phenotypes [4]. Of these, Dpy-19-like 2 (*DPY19L2*) gene, mapping in the long arm of chromosome 12, is the only gene that has been linked to globozoospermia [4].

Globozoospermia is a rare disorder of sperm morphology characterized by round-headed spermatozoa without acrosome, cytoskeleton defects around the nucleus, absence of a post-acrosomal sheath, and the separation of nuclear membranes. The classic form is characterized by 100% round-headed spermatozoa, which are unable to penetrate the oocyte and thus cause primary infertility, and a partial form characterized by the presence of a variable percentage (20%–90%) of morphologically abnormal spermatozoa [5]. NGS has identified several mutations of the *DPY19L2* gene reported to be associated with the globozoospermia phenotype. In addition, mutations in other genes such as spermatogenesis-associated 16 (*SPATA16*), encoding for a protein interacting with C kinase 1 (PICK1), have also been associated with globozoospermia [5].

We herein report the case of a patient with globozoospermia who showed a newly reported variation in the *DPY19L2* gene. In addition, we performed a systematic review of the literature to propose an up-to-date genetic panel for the evaluation of patients with globozoospermia. We also evaluated intracytoplasmic sperm injection (ICSI) outcomes in patients with globozoospermia and the offspring health to offer updated insights for the counseling of patients with globozoospermia seeking fertility. Finally, recommendations on the management of patients with globozoospermia have been made.

This study was conducted at the Division of Endocrinology, Metabolic Diseases and Nutrition of the University-Teaching Hospital Policlinico "G. Rodolico", University of Catania (Catania, Italy). The protocol was approved by the internal Institutional Review Board of the Division of Endocrinology, Metabolic Diseases and Nutrition of the University-Teaching Hospital Policlinico "G. Rodolico", Catania. Written informed consent was obtained from the patient after a full explanation of the purpose and nature of all procedures used. The study has been conducted according to the principles expressed in the Declaration of Helsinki.

CASE REPORT

1. Materials and Methods

1) Semen collection and analysis

Semen collection was performed after 4 days of sexual abstinence. The sample was stored at a temperature of 37°C until the clot liquefied. An experienced and well-trained in semen analysis biologist analyzed the sample. Semen analysis was conducted according to World Health Organization (WHO) 2010 criteria [6]. Briefly, the liquefaction of the sample was constantly evaluated until it was reached. Once liquefied, the appearance, volume, and pH of the seminal fluid were evaluated. At the end of the macroscopic evaluation, the sample was thoroughly mixed and a 10 μL aliquot was withdrawn for evaluation at 10x magnification for the presence of mucoid filaments, round cells, and areas of sperm agglutination or aggregation. Within 60 minutes of collection and at 20× magnification, several 10 μL aliquots of the well-mixed semen sample were evaluated for sperm motility. The final value was given by the average of the different rates counted. The sperm concentration was assessed by the Neubauer chamber. Morphology was assessed according to the strict Kruger criteria after preparation and staining of the seminal fluid smear and observation at 40× magni-

fication.

2) Flow cytometry analysis

The flow cytometry was used to analyze the following bio-functional sperm parameters: chromatin compactness, percentage of apoptotic/alive spermatozoa, mitochondrial membrane potential (MMP), DNA fragmentation. All the assays were performed using the flow cytometer CytoFLEX (Beckman Coulter, IL, Milan, Italy) equipped with two argon lasers and six total fluorescence channels (four 488 nm and two 638 nm), and 100,000 events were measured for each sample and analyzed by the software CytExpert 1.2.

In detail, the evaluation of chromatin compactness was performed after the permeabilization of the cell membrane to allow the penetration of the fluorophore into the nucleus. An aliquot of 1×10^6/mL spermatozoa was incubated with LPR DNA-Prep Reagent (Beckman Coulter, IL), in the dark, at room temperature for 10 minutes, and then further incubated with Stain DNA-Prep Reagent containing 50 μg/mL of propidium iodide (PI) (<0.5%), RNase A (4 KUnitz/mL), <0.1% NaN_3, saline, and stabilizers (Beckman Coulter, IL) in the dark at room temperature. Flow cytometry analysis was performed after 30 minutes.

The percentage of alive spermatozoa and spermatozoa in late or early apoptosis was evaluated by simultaneous incubation of spermatozoa with PI and annexin V labeled with fluorescein isothiocyanate (FITC).

An aliquot containing 0.5×10^6/mL was suspended in 0.5 mL buffer containing 10 μL of annexin V-FITC and 20 μL of PI (Annexin V-FITC Apoptosis; Beckman Coulter IL, Milan, Italy) and incubated for 10 minutes in the dark. After incubation, the sample was analyzed immediately. The different patterns of staining allowed us to identify the different 3 cell populations: viable cells (FITC-negative and PI-negative); cells in early apoptosis with cytoplasmic membrane still intact (FITC positive and PI negative); cells in late apoptosis (FITC-positive and PI-positive).

MMP was evaluated by a lipophilic probe 5,5',6,6'-tetrachloro-1,1',3,3'tetraethyl-benzimidazolylcarbocyanine iodide (JC-1; DBA Srl, Milan, Italy) able to penetrate into mitochondria. Briefly, an aliquot containing 1×10^6/mL of spermatozoa was incubated with JC-1 in the dark, for 10 minutes, at 37°C. At the end of the incubation period, the cells were washed in phosphate buffered saline (PBS) and analyzed. Therefore, the fluorescence changes reversibly from green to orange when the mitochondrial membrane becomes more polarized. In viable cells with normal membrane potential, JC-1 is in the mitochondrial membrane in the form of aggregates emitting in an orange fluorescence, while in the cells with low membrane potential it remains in the cytoplasm in a monomeric form, giving a green fluorescence.

DNA fragmentation was evaluated by the TUNEL assay using the kit Apoptosis Mebstain (DBA Srl) using Terminal Deoxynucleotidyl Transferase (TdT), an enzyme that polymerizes, at the level of DNA breaks, modified nucleotides conjugated to a fluorochrome. To obtain a negative control, TdT was omitted from the reaction mixture; the positive control was obtained pretreating spermatozoa (about 0.5×10^6/mL) with 1 mg/mL of deoxyribonuclease I, not containing RNAse, at 37°C for 60 minutes before staining.

3) Genetic analysis

To assess the genetic etiology of teratozoospermia, the patient was asked for a blood sample for genetic testing. DNA was extracted from peripheral blood using a commercial kit (Samag Blood DNA Extraction Kit; Sacace Biotechnologies Srl, Como, Italy) and used for NGS analysis on a MiSeqIllumina instrument with a custom-made gene panel designed for teratozoospermia. The target regions were enriched by the Illumina Nextera Rapid Capture Enrichment kit (Illumina, SanDiego, CA, USA). The panel consisted of the following genes: *DPY19L2* (OMIM: 613893), *SPATA16* (OMIM: 609856), *PICK1* (OMIM: 605926), and *ZPBP* (OMIM: 608498). The sequences were mapped on the human reference sequence GRCh38. Pathogenic variations were searched in the Human Gene Mutation Database (HGMD professional; http://www.hgmd.cf.ac.uk/ac/index.php) and MASTERMIND (https://www.genomenon.com/mastermind/). Sanger sequencing was used to confirm NGS variants and was also used for studying variant segregation in family members.

4) Analysis of gene mutations

Variants were filtered as follows: 1) variants with minor allele frequency (MAF) less than 1% in 1,000 Genomes (http://www.1000genomes.org/home), EVS (https://evs.gs.washington.edu/EVS/), and GNOMAD (https://gnomad.broadinstitute.org/) databases were considered; 2) the evaluation focused on coding exons

along the flanking ±15 intronic bases; 3) for synonymous and splicing variants with GMAF/MAX MAF lower than the known frequency of the disease, the presence on the database was verified, such as the HGMD. Interpretation of variants is produced by the American College of Medical Genetics and Genomics (ACMG) guideline scoring system. All variants related to the patient's phenotype are reported except for the benign or likely benign variants. The highlighted variants are classified into pathogenic, probably pathogenic, and of uncertain significance. Bioinformatics tools were used to predict pathogenicity *in silico* (such as SIFT, MutationTaster, PROVEAN, Polyphen2) and to evaluate the evolutionary conservation for missense variants.

2. Case presentation

A young couple (25 y the male partner and 22 y the female partner) came to our observation for primary infertility. The couple was seeking pregnancy for 24 months. The male partner was born from non-consanguineous parents, reported smoking (about 20 cigarettes/daily since the age of 15 y), no alcohol consumption, sexual dysfunction, or symptoms of sexually-transmitted diseases. On physical examination, the patient had normal testicular volume (right 25 mL and left 20 mL), palpable deferens, and painful epididymal caput bilaterally. He had also palpable but not visible scrotal varices, no discernible reflux on the Valsalva's maneuver, and second-degree obesity (body mass index 35.6 kg/m^2).

He had never undergone sperm analysis or andrological counseling. We requested an ultrasound examination that showed a right testis volume of 22 mL and a left one of 17 mL. There were neither signs of epididymitis nor of varicocele. Sperm analysis showed normal sperm concentration (63 mil/mL), reduced progressive motility (3%), absolute teratozoospermia with almost 100% round-headed spermatozoa, and leukocytospermia (3.66 mil/mL). Thus, we requested microbiological tests from both partners, which detected the presence of *Ureaplasma urealyticum* infection treated with two cycles of antibiotic and anti-inflammatory therapy. After resolution of the infection, about 3 months after the first sperm analysis, the patient was requested a second exam that confirmed asthenozoospermia (progressive motility 20%) and 100% round-headed teratozoospermia (Fig. 1). The assessment of biofunctional parameters by flow cytometry analysis showed an adequate number of alive spermatozoa and a reduced rate of spermatozoa in late and early apoptosis. Chromatin compaction was normal. However, we found an increased rate of sperm DNA fragmentation. Finally,

Table 1. Conventional and biofunctional sperm parameters of the patient with globozoospermia

Sperm parameter	First collection	Second collection	Normal values
Concentration (mil/mL)	61	100	>15 mil/mL
Total sperm count (mil/ejaculate)	152.5	250	>39 mil/mL
Progressive motility (%)	3	20	>32%
Total motility (%)	55	60	>40%
Normal morphology (%)	0	0	>4%
Leukocytes (mil/mL)	3.66	0.5	<1 mil/mL
Vitality (%)	-	68.2	>60%
Early apoptosis (%)	-	2.7	<10.7%
Late apoptosis (%)	-	7.5	<24.1%
Spermatozoa with chromatin immaturity (%)	-	9.1	<18.9%
DNA fragmentation rate (%)	-	9.5	<4.6%
Spermatozoa with low mitochondrial membrane potential (%)	-	17.6	<11.9%

-: not available.

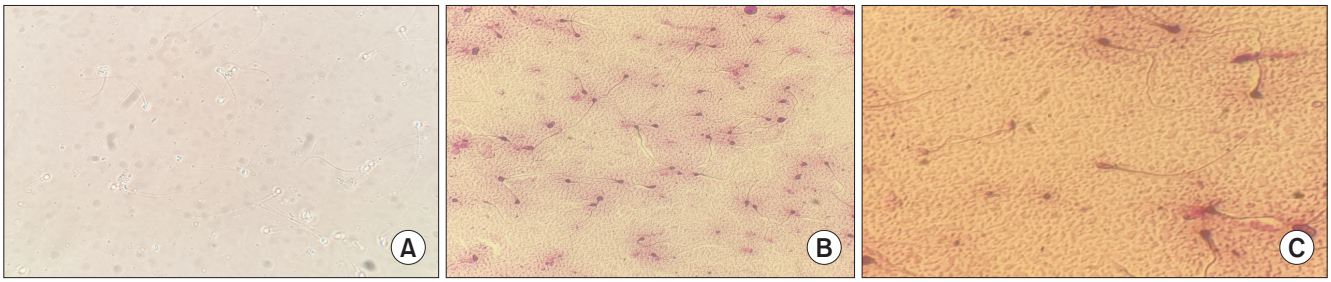

Fig. 1. Fresh sample of the patient's spermatozoa observed under light microscopy at 10× magnification (A), and after staining with hematoxylin-eosin at 10× (B) and 40× magnifications (C).

the rate of spermatozoa with low MMP was increased, thus correlating with the patient's reduced sperm motility (Table 1).

The patient was therefore diagnosed with globozoospermia and underwent blood sampling to search for the possible genetic mutations associated with this condition. The genetic analysis showed the presence of the c. 1688A>C missense mutation of the exon 18 of the *DPY19L2* gene in homozygosity. This mutation results in the substitution of histidine with proline in position 563 of the protein. This variant has never been reported previously and was defined as a variant of uncertain significance due to a lack of *in vitro*/*in vivo* data. However, this variant was considered "pathogenic" or "likely to be pathogenic" in almost all the simulation programs selected for interpretive use. The couple has now been referred to ICSI.

SYSTEMATIC REVIEW

1. Materials and methods

The systematic review was performed by applying the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (Supplement Table 1) [7].

1) Search strategy

The data were extracted through extensive searches in the PubMed, Google Scholar, and Scopus databases from their creation to December 2021.

The search strategy included the combination of the following Medical Subjects Headings (MeSH) terms and keywords: "globozoospermia", "round-headed spermatozoa", "round head spermatozoa", "intracytoplasmic sperm injection", "ICSI", "offspring", "child health", "assisted reproductive technique outcome". The search was limited to human studies and no language restrictions were applied. Studies were first evaluated for inclusion by reading their abstracts. When the abstract did not reveal whether the study contained data relevant to our meta-analysis, the full text was read carefully. The identification of eligible studies was carried out independently by two different researchers (A.C. and R.C.). Any disagreements were resolved by two other researchers (R.A.C. and A.E.C.). Other articles were manually extracted by searching the reference lists of the articles selected by the above keywords.

2) Inclusion and exclusion criteria

All the eligible studies were selected following the PECOS (Population, Exposure, Comparison/Comparator, Outcomes, Study design) model (Supplement Table 2).

We included all the studies that analyzed the impact of genetic abnormalities on the pathogenesis of globozoospermia, the results of ICSI in patients with globozoospermia and of offspring health. We excluded from the analysis comments, letters to the editor, systematic or narrative reviews, animal studies, and studies that did not allow extraction of data on the outcomes of interest. Two investigators (A.C. and R.C) independently evaluated the full text of the studies chosen for eligibility. If any disagreement occurred, a third party (R.A.C. and A.E.C) decided to include or exclude it after discussion.

3) Data extraction and quality assessment

Data were extracted from the eligible studies by two independent authors (A.C. and R.C.). Information on first authors, year of publication, study design, the total number of patients (including the respective controls), type of genetic mutation, sperm aneuploidy rate, and ICSI outcomes was collected. The quality of included studies was independently assessed by two authors (A.C. and R.C.) by applying the "Cambridge Quality Checklists" [8]. Any disagreement between the two investigators was resolved through discussion with other two researchers (A.E.C. and S.L.V.).

The quality and strength of the recommendations provided on the management of the patients with globozoospermia were elaborated using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [9].

2. Results

Using the above-mentioned search strategy, we extracted 884 records. After the exclusion of 246 duplicates, the remaining 638 articles were assessed for inclusion in the systematic review. Of these, 185 were judged not pertinent after reading their title and the abstract, 73 were excluded because they were reviews (n=54), comments (n=3), conference papers (n=10), book chapters (n=5), and letters to the editor (n=1). Finally, 278 articles were excluded because were animal studies. The remaining 102 articles were carefully read. Based on the inclusion and exclusion criteria, 9 articles were excluded because of the inability to extract the

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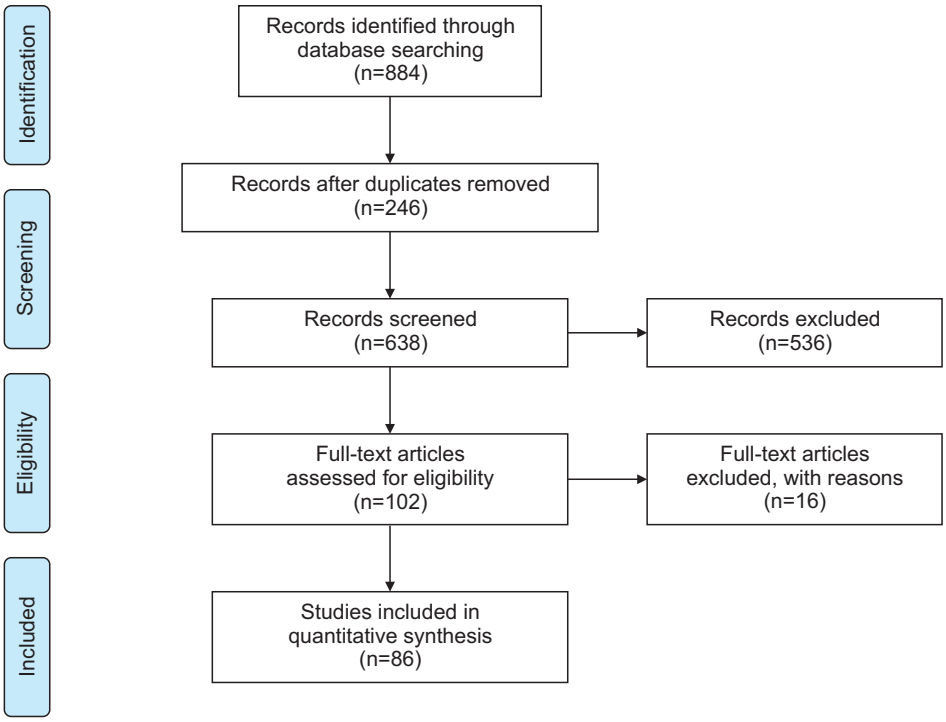

Fig. 2. Flow chart of the studies included in the systematic review.

Table 2. Evaluation of studies quality using "The Cambridge Quality Checklists"

Reference	Checklist for correlates	Checklist for risk factors	Checklist for causal risk factors	Total
Abdelhedi et al, 2019 [26]	1	1	1	3/15
Abdelmoula et al, 2006 [27]	2	1	1	4/15
Alimohammadi et al, 2020 [28]	2	1	2	5/15
Battaglia et al, 1997 [59]	2	1	1	4/15
Bechoua et al, 2009 [60]	1	1	1	3/15
Bourne et al, 1995 [61]	2	1	1	4/15
Brahem et al, 2011 [29]	2	1	2	5/15
Canepa et al, 2019 [62]	2	1	1	4/15
Carrell et al, 1999 [30]	2	1	1	4/15
Celse et al, 2021 [31]	2	1	1	4/15
Chen et al, 2021 [96]	2	1	1	4/15
Cheung et al, 2021 [97]	2	1	1	4/15
Chianese et al, 2015 [98]	1	1	1	3/15
Christensen et al, 2006 [32]	2	1	1	4/15
Coutton et al, 2012 [33]	2	1	2	5/15
Dam et al, 2007 [99]	2	1	2	5/15
Dam et al, 2012 [63]	2	1	2	5/15
Dirican et al, 2008 [64]	2	1	1	4/15
Ditzel et al, 2005 [34]	2	1	2	5/15
Edirisinghe et al, 1998 [65]	2	1	1	4/15
Egashira et al, 2009 [66]	2	1	1	4/15
Elinati et al, 2016 [36]	2	1	1	4/15
Elinati et al, 2012 [35]	2	1	2	5/15
Escoffier et al, 2015 [67]	2	1	1	4/15
Faja et al, 2021 [37]	2	1	2	5/15
Gatimel et al, 2013 [68]	1	1	1	3/15
Ghédir et al, 2016 [38]	2	1	2	5/15

Table 2. Continued 1

Reference	Checklist for correlates	Checklist for risk factors	Checklist for causal risk factors	Total
Ghédir et al, 2019 [39]	2	1	2	5/15
Gunalp et al, 2001 [41]	2	1	1	4/15
Guo et al, 2019 [40]	1	1	2	4/15
Han et al, 2021 [69]	1	1	1	3/15
Harbuz et al, 2011 [42]	2	1	2	5/15
Huang et al, 2010 [70]	1	1	1	3/15
Jiang et al, 2015 [71]	2	1	2	5/15
Jin et al, 2017 [72]	2	1	1	4/15
Kamiyama et al, 2012 [73]	2	1	1	4/15
Karaca et al, 2014 [100]	1	1	1	3/15
Karaca et al, 2015 [74]	2	1	1	4/15
Kashir et al, 2012 [75]	2	1	2	5/15
Khalili et al 1998 [76]	2	1	1	4/15
Kilani et al, 1998 [77]	1	1	1	3/15
Kilani et al, 2004 [78]	1	1	1	3/15
Kim et al, 2001 [79]	1	1	1	3/15
Kochhar and Ghosh, 2018 [80]	2	1	1	4/15
Koscinski et al, 2011 [101]	1	1	1	3/15
Kuentz et al, 2013 [102]	2	1	1	4/15
Kyono et al, 2009 [81]	2	1	1	4/15
Li et al, 2018 [103]	2	1	1	4/15
Li et al, 2020 [43]	1	1	1	3/15
Li et al, 2021 [104]	2	1	1	4/15
Liu et al, 1995 [82]	2	1	1	4/15
Liu et al, 2017 [105]	2	1	1	4/15
Liu et. al, 2010 [44]	2	1	1	4/15
Luo et al, 2020 [45]	2	1	1	4/15
Martin et al, 2003 [46]	1	1	2	4/15
Modarres et al, 2016 [106]	2	1	2	5/15
Moradan and Yousefi, 2014 [83]	1	1	1	3/15
Morel et al, 2004 [47]	2	1	2	5/15
Nardo et al, 2002 [84]	1	1	1	3/15
Noveski et al, 2013 [48]	2	1	1	4/15
Oud et al, 2020 [49]	2	1	1	4/15
Paci et al, 2017 [107]	1	1	1	3/15
Perrin et al, 2011 [50]	2	1	2	5/15
Pirrello et al, 2005 [108]	2	1	2	5/15
Rafaee et al, 2020 [51]	2	1	2	5/15
Ren et al, 2020 [52]	2	1	1	4/15
Roozbahani et al, 2017 [53]	2	1	2	5/15
Sahu et al, 2010 [85]	1	1	1	3/15
Schmiady et al, 2007 [54]	2	1	2	5/15
Sermondade et al, 2011 [86]	2	1	1	4/15
Shang et al, 2019 [109]	2	1	1	4/15
Stone et al, 2000 [87]	1	1	1	3/15
Taskiran et al, 2006 [55]	2	1	1	4/15
Tavalaee et al, 2016 [88]	2	1	1	4/15
Tavalaee et al, 2018 [89]	2	1	1	4/15
Tejera et al, 2008 [110]	2	1	1	4/15

Table 2. Continued 2

Reference	Checklist for correlates	Checklist for risk factors	Checklist for causal risk factors	Total
Tesarik et al, 2002 [90]	2	1	1	4/15
Trokoudes et al, 1995 [91]	1	1	1	3/15
Vicari et al, 2002 [56]	2	1	2	5/15
Vozdova et al, 2014 [111]	2	1	2	5/15
Wu et al, 2013 [57]	1	1	1	3/15
Yassine et al, 2015 [92]	2	1	1	4/15
Zeyneloglu et al, 2002 [93]	1	1	1	3/15
Zhang et al, 2016 [94]	2	1	1	4/15
Zhioua et al, 2011 [95]	1	1	1	3/15
Zhu et al, 2013 [58]	2	1	2	5/15

data required [10-18], whereas 7 were excluded because evaluated the presence of genetic abnormalities and the ICSI outcomes in a population of infertile males, among which patients with globozoospermia were also present without the possibility of extracting specific data only for these patients [19-25] (Supplement Table 3).

Finally, 86 articles met our inclusion criteria and, therefore, were included in this systematic review (Fig. 2) [26-111]. In detail, 33 articles evaluated only the genetic outcome [26-58], 37 articles evaluated only the ICSI outcomes [59-95], and 16 evaluated both outcomes [96-111]. Using the aforementioned search strategy, no studies reported data on offspring's health. However, studies that evaluated the ICSI outcomes also gave some information on the offspring health in case of the success of the ART procedure. All studies were judged to be of low quality after the assessment with the Cambridge Quality Checklists (Table 2).

1) Genetic etiology of globozoospermia

A total of 49 articles evaluated the prevalence and type of genetic abnormalities present in patients with globozoospermia [26-58,96-111] (Table 3). The gene more frequently involved in the pathogenesis of globozoospermia is *DPY19L2* and the mutation most frequently described is the deletion of the entire gene that, which has been reported to have a prevalence ranging from 22.2% [98] to 83.3% [105]. The discrepancy may be due to the difficulty in the identification of the percentage of patients with total or partial form globozoospermia among the studies. Indeed, the highest prevalence of the mutation occurs in studies reporting total globozoospermia. On the other hand, mutations in this gene seem to play a minor role in partial globozoospermia. Studies where patients with partial globozoospermia can be clearly distinguished from those with total globozoospermia [33,38,106,107] rarely report a heterozygous mutation of the *DPY19L2* gene, such as the deletion of an allele [38,106]. While in most cases, no mutation was found in these patients [33,38,106,107]. Among other mutations of *DPY19L2* associated with globozoospermia, homozygous or compound heterozygous deletions of some exons have been reported. These include the involvement of exons 5, 6, 7, 10, 11, 12, and 22 [29,36,37,45,98,106]. In other cases, point mutations or few nucleotide deletions in both homozygosity and compound heterozygosity, together with other point mutations or deletions of the *DPY19L2* gene have been described [31,33,35,38,52,58,104,109]. Finally, in a percentage ranging from 8.3% [105] to 55.6% [97] of cases, no mutation in the *DPY19L2* gene is identified. The important variability likely depends on the inclusion of patients with total or partial globozoospermia. In these cases, other genes have been called into play in the pathogenesis of globozoospermia, such as *SPATA16*. To date, only 5 studies described mutations of *SPATA16* [36,39,97,99,100]. Two studies have only specified the presence of the mutation of this gene as a cause of globozoospermia but the type of mutation was not reported [97,100]. Two other studies described the homozygous deletion of exon 2 of the gene [36,39], and the last one described the presence of the homozygous point mutation c. 848 G>A in exon 4 in three brothers with globozoospermia [99]. Only two studies have described a role for the *PICK1* gene in the pathogenesis of globozoospermia. One study described a patient affected by a mutation of this gene without specifying its type [97],

Table 3. Studies evaluating the presence of genetic mutations in the pathogenesis of globozoospermia

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Abdelhedi et al, 2018 [26]	Case-control	5 globozoospermic patients and 5 controls	*DPY19L2*	Homozygous deletion of the gene (3 patients); composite heterozygous mutations (2 patients)	-
Abdelmoula et al, 2020 [27]	Cross-sectional	34 infertile patients (16 oligozoospermic and 18 azoospermic)	*DAZ*	*DAZ* deletion in 4 patients and 1 had high prevalence of round head spermatozoa	-
Alimohammadi et al, 2020 [28]	Case-control	63 patients with globozoospermia (29 with total and 34 with partial globozoospermia) and 41 fertile controls	*DPY19L2*	Homozygous deletion in 22/29 patients with total globozoospermia, none in those with partial globozoospermia Homozygous deletion of exon 7 in 2/7 patients with complete globozoospermia without total deletion of the gene No role for polymorphisms	-
Brahem et al, 2010 [29]	Cross sectional	2 patients with globozoospermia	-	-	Sex chromosome aneuploidy and disomy 8
Carrell et al, 1999 [30]	Case report	2 patients with globozoospermia	-	-	High aneuploidy rate of chromosome 21 in sibling 1 and high aneuploidy rate of heterochromosomes and chromosomes 3 and 21 in sibling 2
Celse et al, 2021 [31]	Cross-sectional	69 patients with total or partial (>20%) globozoospermia	*DPY19L2*	Homozygous deletion of the entire gene (25 patients) Heterozygous deletion of one allele and other point mutation in the remaining allele: · Frameshift mutation in exon 11 c.1183delT (1 patient) · Non sense mutation in exon 19 c.1840G>T (1 patient) · Splice site mutation in intron 16 c.1580+1G>A (1 patient) · Missense mutation in exon 8 c.869G>A (2 patients) · Missense mutation in exon 4 c.586G>C (1 patient) · Missense mutation in exon 4 c.575A>G (1 patient) · Missense mutation in exon 8 c.925C>A (1 patient) Homozygous frameshift mutation in exon 1 c.153_189del (1 patient) Homozygous missense mutation in exon 8 c.892C>T (3 patients) Homozygous missense mutation in exon 8 c.893G>A (1 patient) Homozygous missense mutation in exon 14 c.1438G>A (1 patient)	-
			GGN	Homozygous frameshift mutation in exon 3 c. 416_437del (1 patient with partial globozoospermia)	

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Table 3. Continued 1

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Chen et al, 2021 [96]	Case-control	2 brothers with globozoospermia	*SPACA1*	A nonsense variant c.53G>A	-
Cheung at al. 2021 [97]	Observational before-after	4 patients with partial and 10 with complete globozoospermia Genetics evaluated only in 3 patients with complete globozoospermia	*DPY19L2* *SPATA16* *PICK1*	Point mutation Point mutation Point mutation	Aneuploidy rate of 2.1% (±2) in patients with partial globozoospermia, with main involvement of chromosomes 18 and 22, instead aneuploidy rate of 5.5% (±1) in patients with complete globozoospermia with prevalent involvement of chromosomes 13, 15, 16, and 18
Chianese et. al, 2015 [98]	Cross-sectional	9 patients with variable degree of globozoospermia	*DPY19L2*	Homozygous deletion (2 patients) Heterozygous compound with deletion of one allele and deletion of exon 7 in second allele (1 patient) Heterozygous c. 494 C>T (1 patient) - likely pathogenetic Remaining patients had SNPs likely to be non-pathogenic	-
Christensen et al, 2006 [32]	Case control	2 patients with partial globozoospermia and 12 fertile controls	*HRB*	6 polymorphisms (4 in intron region e 1 in exon 4 and 1 in exon 12). Only heterozygous 39 T/C polymorphism was found in one patient with globozoospermia and in none of controls. However, no causal effect can be established	-
			GOPC	5 polymorphisms in intron region. However, no causal effect can be established	
			CSNK2A2	4 polymorphisms in intron region. However, no causal effect can be established	
Coutton et al, 2012 [33]	Cross-sectional	34 patients with globozoospermia	*DPY19L2*	Homozygous deletion in 23 patients Heterozygous deletion in 2 patients and other point mutations in the remaining allele: · Heterozygous missense mutation in exon 8 c.869G>A · Heterozygous nonsense mutation in exon 9 c.1024C>T Homozygous missense mutation in exon 10 c.1073T>A All these variants were considered likely to be pathogenic in *in silico* analysis	-
Dam et al, 2007 [99]	Cross-sectional	3 of six brothers affected by globozoospermia	*SPATA16*	Homozygous point mutation c.848G>A in exon 4	-

Table 3. Continued 2

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Ditzel et al, 2005 [34]	Case-control	1 patient with globozoospermia and 10 controls	-	-	Patient with globozoospermia presented a higher rate of aneuploidy of chromosomes 13, 16, and 21 than controls (18% *vs*. 2.52%)
Faja et al, 2021 [37]	Case control	18 patients with globozoospermia (10 complete and 8 partial globozoospermia) and 32 fertile controls	*DPY19L2*	Deletion of exon 11 (1 patient) Deletion of exon 22 (1 patient) Deletion of exon 10, 12, and 22 (4 patients)	-
Ghédir et al, 2016 [38]	Cross-sectional	14 genetically independent patients with total globozoospermia	*DPY19L2*	Homozygous deletion of the entire gene (11 patients) Homozygous c.892C>T (2 patients) Homozygous c.1579_1580+4delAGGTAAinsTCAT (1 patient)	-
		4 genetically independent patients with partial globozoospermia		Heterozygous deletion of the gene (1 patient)	
Ghédir et al, 2019 [39]	Case-control	8 patients with total globozoospermia and 25 fertile controls	*DPY19L2* *SPATA16*	Homozygous deletion of the entire gene (6 patients) Deletion of exon 2 (2 patients)	Aneuploidy rate higher in patients with globozoospermia and higher in patients with *SPATA16* gene mutation than control The group with *SPATA16* mutation showed a higher rate of heterochromosome and chromosome 18 dysomies.
Guo et al, 2019 [40]	Cross-sectional	3 patients with total globozoospermia	*DPY19L2*	Homozygous deletion	-
Gunalp et al, 2001 [41]	Case-control	12 patients with total globozoospermia and 10 fertile controls	Y chromosome	No role for microdeletion in pathogenesis of globozoospermia	-

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Table 3. Continued 3

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Elinati et al, 2012 [35]	Cross-sectional	54 genetically independent patients with globozoospermia	*DPY19L2*	Homozygous deletion in 25 patients Heterozygous deletion with combined mutation in second allele: · c.869G>A variation in exon 8 · c.1033C>T introducing a premature stop codon, in exon 9 · c.1478C>G leading to a non-synonymous mutation in exon 15 · c.2038A>T introducing a premature stop codon in exon 21 · c.1183delT introducing a premature stop codon in exon 11 (2 patients) · Deletion of exons 5 and 6 Homozygous c.892C>T leading to a non-synonymous mutation in exon 8 Homozygous donor splice-site mutation c.1218+1G>A in intron 11 Homozygous deletion of exons 5 and 6 Deletion of exons 5, 6, and 7	-
Elinati et al, 2016 [36]	Cross-sectional	19 patients with globozoospermia negative for DPY19L2 mutations	*SPATA16*	Deletion of exon 2 (2 patients)	-
Harbuz et al, 2011 [42]	Cross-sectional	20 patients with total globozoospermia	*DPY19L2*	Homozygous deletion (15 patients)	-
Karaca et al, 2014 [100]	Case report	1 patient with total globozoospermia	*SPATA16*	Not specified homozygous mutation	-
Koscinski et al, 2011 [101]	Cross-sectional	4 patients with complete globozoospermia (brothers)	*DPY19L2*	Deletion of the whole gene	-
Kuentz et al, 2013 [102]	Cross sectional	32 patients with complete globozoospermia and 2 with partial globozoospermia	*DYP19L2*	Gene mutated in 29 patients without specification of the type of mutation	-
Li et al, 2018 [103]	Case report	1 patient with combined globozoospermia and acephalic spermatozoa	*DNAH6*	Compound heterozygote c.2454A>T and c.7706G>A – likely pathogenic	-
Li et al, 2020 [43]	Case-report	1 patient with complete globozoospermia	*DPY19L2*	180-kbp homozygote deletion at 12q14.2 which include the complete deletion of DPY19L2	-

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Table 3. Continued 4

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Li et al, 2021 [104]	Cross-sectional	149 infertile patients 16 of which with total or almost total globozoospermia	*DPY19L2*	Compound heterozygous with deletion of one allele and frameshift mutation c.1561del (1 patient with total globozoospermia)	-
			PIWIL4	Compound heterozygous missense mutations c.1861G>A and c.2503C>A (probably causative) (1 patient with almost total globozoospermia)	
			CCNB3	Hemizygous frameshift mutation c.1862dup (probably causative) (1 patient with total globozoospermia)	
			CHPT1	Homozygous frameshift mutation c.715dup (probably causative) (1 patient with almost total globozoospermia)	
Liu et al, 2010 [44]	Cross-sectional	3 patients with globozoospermia screened for *GOPC*, *HRB*, *CSNK2A2*, and *PICK1* mutations	*PICK1*	Homozygous missense mutation c.1567G>A in exon 13 of the *PICK1* gene (1 patient)	-
Liu et al, 2017 [105]	Case report	1 patient with globozoospermia	*DPY19L2*	Homozygous deletion	-
Luo et al, 2020 [45]	Case report	2 patients with globozoospermia	*DPY19L2*	Homozygous deletion of 5, 6, and 15 exons	-
Martin et al, 2003 [46]	Case-control	1 patient with globozoospermia and 5 healthy controls	-	-	Higher XY disomy rate in spermatozoa of patients with globozoospermia than controls (0.38% *vs*. 0.15%)
Modarres et al, 2016 [106]	Case-control	24 patients with total globozoospermia	*DPY19L2*	Homozygous deletion (20 patients) Partial deletion exon 5, 6, and 7 (2 patients)	-
		3 patients with partial globozoospermia		No deletion	
Morel et al, 2004 [47]	Case-control	2 patients with complete globozoospermia and 4 controls	-	-	Patient 1 presented significantly higher disomy rate of 13 and 21 chromosomes than controls and patient 2. No difference between patient 2 and controls
Noveski et al, 2013 [48]	Cross sectional	2 patients with globozoospermia	*DIP19L2*	Homozygous deletion	-

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Table 3. Continued 5

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Oud et al, 2020 [49]	Cross-sectional	15 patients with globozoospermia and no conclusive diagnosis after analysis in the *DPY19L2* and *SPATA16* genes	*ZPBP*	Homozygous nonsense mutation c.931C >T - likely pathogenic because knockout in this gene is already known as a cause of globozoospermia in mouse	-
			CCDC62	Homozygous nonsense variant c.442C >T - likely pathogenic because mutation in this gene is already known as a cause of globozoospermia in mouse	
			C2CD6	Homozygous missense variant c.338A >G - uncertain significance but possible causative because this gene is related to acrosome biology	
			CCIN	Homozygous missense variant c.853G >A - uncertain significance but possible causative because this gene is related to acrosome biology	
			C7orf61	Homozygous frameshift variant c.259del - uncertain significance but possible causative because this gene is related to acrosome biology	
			GGN	Homozygous frameshift mutation c.1271del (2 patients) - possible causative because this gene is related to infertility	
			DNAH17	Two heterozygous missense variants c.2830C >T and c.7780 T >A - possible causative because this gene is related to infertility	
Paci et al, 2017 [107]	Cross-sectional	3 patients with total globozoospermia 1 patient with partial globozoospermia	*DPY19L2* *DPY19L2*	Homozygous deletion (3 patients) Heterozygous deletion (1 patient)	-
Perrin et al, 2011 [50]	Case control	1 patient with globozoospermia	-	-	Significant higher disomy of 21, X, and Y chromosomes than controls
Pirrello et al, 2005 [108]	Case control	6 patients with globozoospermia and 10 controls	*CSKN2A2* *CSKN2B*	No mutations No mutations	Only one patient was screened for aneuploidy of 1, X, and Y chromosome with a normal rate of aneuploidy
Rafaee et al, 2020 [51]	Case-control	90 normozoospermic men and 30 teratozoospermic patients	*SEPT12*	c.512+71A>G SNP higher prevalence in patients with globozoospermia (n=30), but not statistically significant compared to controls	-
Ren et al, 2020 [52]	Case report	2 brothers with globozoospermia	*DPY19L2*	Heterozygous compound: · Deletion of the whole gene · c. 384dup	-
Roozbahani et al, 2017 [53]	Case-control	130 patients with teratozoospermia and globozoospermia and 110 fertile controls	*SPATA16*	SNP rs137853118 located in exon 4 of SPATA16 gene not related to globozoospermia	-

Table 3. Continued 6

Reference	Type of study	Population	Involved gene	Mutations	Sperm aneuploidy
Schmiady et al, 2007 [54]	Case report	1 patient with globozoospermia	-	-	No increase in aneuploidy rate in the globozoospermic patient compared with 5 controls obtained from literature
Shang et al, 2019 [109]	Cross-sectional	9 patients with total globozoospermia	*DPY19L2*	DPY19L2 deletions in 5 patients and the other four patients contained novel DPY19L2 point mutations: · Heterozygous variant (c.2126+5G>A) · Homozygous nonsense mutation (c.1720C>T · Compound heterozygous variants (c.1182-1184delATC, c.368A>T · Compound heterozygous deletion (c.1182-1184delATCTT, and two-nucleotide deletion c.1553-1554delAT)	-
Taskiran et al, 2006 [55]	Cross-sectional	12 patients with complete globozoospermia	Y microdeletions	No role of Y microdeletions in pathogenesis of globozoospermia	-
Tejera et al, 2008 [110]	Case report	1 patient with complete globozoospermia	-	-	Slightly but significantly higher aneuploidy rate in the globozoospermic patient compared to controls obtained from literature
Vicari et al, 2002 [56]	Caser report	1 patient with complete globozoospermia	-	-	Aneuploidy rate similar between patient and controls
Vozdova et al, 2014 [111]	Case-control	1 patient with complete globozoospermia and 10 healthy controls	-	-	Higher XX and XY disomy rate in globozoospermic patients than controls
Wu et al, 2013 [57]	Case report	1 patient with globozoospermia	*DPY19L2*	No mutation	-
Zhu et al, 2013 [58]	Case-control	15 unrelated patients with total globozoospermia and 100 fertile patients	*DPY19L2*	Homozygous for deletion (4 patients) Heterozygous for deletion without mutations in the other allele (1 patient) Homozygous c.1532delA in exon 15 causing a frameshift mutation (2 patients) Homozygous multi-mutation in exon 18 consisting of a nucleotide deletion c.1679delT and a two-nucleotide deletion c.1681_1682delAC (c.[1679delT; 1681_1682delAC]) (1 patient) Homozygous for c.869G>A missense mutation in exon 8 (1 patient) Homozygous missense mutation c.989T>C in exon 9 (1 patient)	-

C2CD6: C2 calcium-dependent domain-containing 6, *C7orf61*: chromosome 7 open reading frame 61, *CCDC62*: coiled-coil domain containing 62, *CCIN*: calicin, *CCNB3*: cyclin B3, *CHPT1*: choline phosphotransferase 1, *CSNK2A2*: casein kinase 2 alpha 2, *CSNK2B2*: casein kinase 2 beta 2, *DAZ*: deleted in azoospermia, *DNAH17*: dynein axonemal heavy chain 17, *DNAH6*: dynein axonemal heavy chain 6, *DPY19L2*: Dpy-19-like 2, *GGN*: gametogenetin, *GOPC*: Golgi-associated PDZ and coiled-coil motif-containing protein, *HRB*: HIV-1 Rev-binding protein, *PICK1*: protein interacting with C kinase 1, *PIWIL4*: piwi like RNA-mediated gene silencing 4, *SEPT12*: septin 12, *SPACA1*: sperm acrosome membrane-associated protein 1, *SPATA16*: spermatogenesis-associated 16, *ZPBP*: zona pellucida binding protein.

while another identified the homozygous missense mutation c.1567G>A in exon 13 of the gene, in one of three patients belonging to a Chinese family screened for the mutation of this gene [44]. Several other genes have been investigated to explain the possible pathogenesis of globozoospermia with often inconclusive results. In particular, the role of Y chromosome mutations or Y chromosome microdeletions has been evaluated in two studies, but no correlation resulted [41,55]. In the case report by Li and colleagues, on a patient with globozoospermia and acephalic sperm, a compound heterozygote mutation (c.2454A>T and c.7706G>A) of the dynein axonemal heavy chain 6 (*DNAH6*) gene was found and considered as likely pathogenic [103].

Oud and colleagues studied the mutations of different genes in 15 patients with globozoospermia. No conclusive diagnosis resulted after analysis of the *DPY19L2* and *SPATA16* genes. The authors found mutations in 7 new genes considered as possible candidates in the pathogenesis of globozoospermia since they cause globozoospermia in mouse models (zona pellucida binding protein [*ZPBP*] and coiled-coil domain containing 62 [*CCDC62*] genes), or because they are involved in acrosome biology (C2 calcium-dependent domain-containing 6 [*C2CD6*], calicin [*CCIN*], and chromosome 7 open reading frame 61 [*C7orf61*] genes), or because they have a relevant role in fertility (*DNAH17* and gametogenetin [*GGN*] genes) [49]. Also, another study identified a homozygous frameshift mutation c.416_437del in exon 3 of *GGN* gene in 1 patient with partial globozoospermia, suggesting a role for this gene in the pathogenesis of this disease [31].

Recently, Li and colleagues described possible causative gene variations in 3 new genes. In detail, they found a mutation in the cyclin B3 gene (*CCNB3*), which causes globozoospermia also in mouse models. Moreover, they found mutations in the piwi like RNA-mediated gene silencing 4 (*PIWIL4*) and in the choline phosphotransferase 1 (*CHPT1*) gene, both related to acrosomal biogenesis [104].

Even casein kinase 2 alpha and 2 beta (*CSKN2A2* and *CSKN2B*) genes were evaluated in a study on 6 patients with globozoospermia, but no mutations were found [108]. Christensen and colleagues studied the possible role of HIV-1 Rev-binding protein (*HRB*), golgi-associated PDZ and coiled-coil motif-containing protein (*GOPC*), and *CSNK2A2* genes polymorphism, without finding a correlation [32]. Also, the role of polymorphisms of the septin 12 (*SEPT12*) gene was investigated without finding a link with globozoospermia [51]. Finally, Chen et al [96] described a nonsense variant c.53G>A in sperm acrosome membrane-associated protein 1 (*SPACA1*) gene in 2 brothers with globozoospermia, suggesting a possible pathogenetic role for this gene.

2) Sperm aneuploidy rate in patients with globozoospermia

Fourty-eight articles evaluated the genetic background of patients with globozoospermia [26-58,97-111]. Among these, we searched for the rate of sperm aneuploidies to assess the possible risk of transmission of genetic abnormalities to offspring (Table 3). Patients with globozoospermia seem to have a higher rate of sperm aneuploidies compared with controls [29,30,34,46,47,50,97,110,111]. In particular, the chromosomes mainly involved seem to be the 13, 16, 18, 21, and the heterochromosomes [30,34,39,46,47,50,111]. A single study has also shown a higher rate of aneuploidy of chromosome 8 [29] and another of chromosomes 15 and 22 [98]. Moreover, in patients with partial globozoospermia, the rate of aneuploidy seems to be lower than in those with the complete form [98]. Finally, one study showed a higher rate of aneuploidies in the patient with mutations of the *SPATA16* gene than in other patients with complete globozoospermia [39]. In contrast, only three studies found no difference in the sperm aneuploidies rate between cases and controls [54,56,108].

3) ICSI outcomes in patients with globozoospermia

Table 4 summarizes the data extracted from studies evaluating ICSI outcomes. The main compromised outcome in patients with globozoospermia is the fertilization rate that is lower than in patients undergoing ICSI without globozoospermia [111]. In detail, the mean fertilization rate for studies including only patients with total globozoospermia is 24.1% (±21.7%) with a wide variability between studies [59-61,64-68,76,78,82,84,85,87,90-94,96,102,104,105,110,111]. The fertilization rate is higher in patients with partial globozoospermia (61%±29.1%) [62,63,77,94,104]. This mean fertilization rate, resulted similar to that found in patients without globozoospermia in two studies comparing patients with partial globozoospermia and controls without globozoospermia [63,71]. In contrast, the success

Table 4. Studies evaluating the outcomes of assisted reproductive techniques

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Battaglia et al, 1997 [59]	Case report	1 patient with complete globozoospermia	Conventional ICSI (first cycle)	1/18	-	-	-	0	-
			Conventional ICSI (second cycle)	2/20	-	-	-	0	-
			ICSI+AOA	6/8	-	-	-	0	-
Bechoua et al, 2009 [60]	Case report	3 patients with complete globozoospermia	ICSI	26/44	Yes	5/9 embryos transferred	1 spontaneous abortion and 1 therapeutic abortion for isochromosome 12	2/5 clinical pregnancies	-
Bourne et al, 1995 [61]	Case report	1 patient with complete globozoospermia	ICSI	3/7	-	0/2 embryos transferred	-	0	-
Canepa et al, 2019 [62]	Case report	1 patient with partial globozoospermia	Conventional ICSI	2/7	-	0	-	-	-
			Hyaluronic acid ICSI (first cycle)	4/7	Yes	1/2 embryos transferred	-	1 clinical pregnancies	2 grade A embryos
			Hyaluronic acid ICSI (second cycle)	10/14	Yes	1/2 embryos transferred	-	-	Grade 1 and grade 3BB embryos
Chianese et. al, 2015 [98]	Case series	9 patients with variable degree of globozoospermia	ICSI	7/32	-	0/7 embryos transferred			
Chen et al, 2021 [96]	Case report	1 patient with total globozoospermia	ICSI	2/18	-	-	-	-	-
		1 patient with total globozoospermia	IMSI	12/32	YES	0/7 embryos transferred	-	-	-

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Table 4. Continued 1

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Cheung et al, 2021 [97]	Cross-sectional	4 patients with partial globozoospermia and 10 patients with complete globozoospermia	Conventional ICSI (14 patient)	35/268	YES	1/19 embryos transferred	1/1		-
			Repetition of Conventional ICSI (4 patient with OASCF)	43/119	Yes 4/20 embryos transferred	2/20 embryos transferred	1/5 clinical pregnancies	2/2 clinical pregnancy	
			ICSI with AGT (7 patient without OASCF)	39/97	Yes 6/21 embryos transferred	5/21 embryos transferred		4/5 clinical pregnancies	
Dam et al, 2007 [99]	Case report	2 of 3 brothers affected by globozoospermia and *SPATA16* mutation	Conventional ICSI	-	-	-	-	0	-
Dam et al, 2012 [63]	Case control	27 patients with partial globozoospermia	ICSI	Median per cycle 75%	Yes	21 clinical pregnancies	3/21 pregnancies	18/21 pregnancies of which 3 twin pregnancies and 15 singleton pregnancies	Median of quality A embryos 67%
		263 controls	ICSI	Median per cycle 75%	Yes	162 clinical pregnancies	30/162 pregnancies	132/162 of which 35 twin pregnancies and 97 singleton pregnancies	Median of quality A embryos 47%
Dirican et al, 2008 [64]	Case report	2 patients with complete globozoospermia	ICSI	1/11 (9.1%)	Yes	1/1 embryos transferred	-	1/1 clinical pregnancy	Grade I embryos
			ICSI+AOA	2/6 (33.3%)	Yes	1/2 embryos transferred	-	1/1 clinical pregnancy	Grade I embryos
Edirisinghe et al, 1998 [65]	Case report	1 patient with complete globozoospermia	ICSI	2/24	-	0/2 embryos transferred	-	-	Grade 2/4 and 3/4

Table 4. Continued 2

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Egashira et al, 2009 [66]	Case report	1 patient with complete globozoospermia	ICSI	0/2	-	-	-	-	-
			ICSI+electrical AOA	7/7	Yes	1/2 embryo transferred	-	1/1 clinical pregnancy	-
Escoffier et al, 2015 [67]	Cross sectional	9 patients with complete globozoospermia	ICSI	17/139	-	-	-	-	-
Gatimel et al, 2013 [68]	Case report	2 patients with complete globozoospermia	ICSI	1/13	Yes	1/1 embryo transferred	-	1/1 clinical pregnancy	1 high quality embryo
Han et al, 2021 [69]	Case series	5 patients with almost complete globozoospermia	ICSI	-	-	-	1	1	-
Huang et al, 2010 [70]	Case report	1 patient with globozoospermia	ICSI	4/19	-	1/2 embryo transfers	-	1/1 clinical pregnancy	-
Jiang et al, 2015 [71]	Case control	34 patients with partial globozoospermia	IVF	25.4±17.4	Yes	6/11 embryos transferred	-	-	47.4±25.2 (rate of high-quality embryos)
			ICSI	66.2±22.5	Yes		-	-	
		60 controls	IVF	70.3±24.3	Yes	8/14 embryos transferred	-	-	45.3±27.1 (rate of high-quality embryos)
			ICSI	68.8±29.4	Yes		-	-	
Jin et al, 2017 [72]	Case report	1 patient with complete globozoospermia	Hard activation ICSI	7/31	Yes	3/4 embryos transferred	-	3/3 clinical pregnancies	4 embryos of high quality
Kamiyama et al, 2012 [73]	Case report	1 patient with partial globozoospermia	ICSI+AOA with Ca^{++} ionophore	4/5	Yes	1/2 embryos transferred	-	1/1 clinical pregnancy	-
Karaca et al, 2014 [100]	Case report	1 patient with total globozoospermia and *SPATA16* mutation	ICSI+AOA	1/12	Yes	1/1	-	1/1 clinical pregnancy	-

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Table 4. Continued 3

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Karaca et al, 2015 [74]	Case report	1 patient with complete globozoospermia	ICSI	5/53	-	0/5 embryo transferred	-	-	-
			ICSI+AOA with Ca^{++} ionophore for 7 minutes	2/4	-	-	-	-	-
			ICSI + AOA with Ca^{++} ionophore for 14 minutes	3/5	Yes	1/2 embryo transferred	-	1/1 clinical pregnancy	-
Kashir et al, 2012 [75]	Case report	3 patients with complete globozoospermia	IMSI without AOA	9/18	-	-	-	-	-
			IMSI with AOA	13/23	-	-	-	-	-
Khalili et al, 1998 [76]	Case series	4 patients with complete globozoospermia	Conventional ICSI	0/22	-	-	-	-	-
Kilani et al, 1998 [77]	Case report	1 patient with partial globozoospermia	ICSI	13/20	Yes	4/7 embryo transfer (all of the same ICSI cycle)	1/4 clinical pregnancies	3/4 clinical pregnancies (triplet pregnancy)	-
Kilani et al, 2004 [78]	Case series	5 brothers with complete globozoospermia	ICSI	49/129 (38%)	Yes	3/44 embryo transferred	2/3 clinical pregnancies lost in first trimester	1/3 clinical pregnancies	
Kim et al, 2001 [79]	Case report	1 patient with complete globozoospermia and mosaic Down syndrome	ICSI+AOA with Ca^{++} ionophore	21/35 (60%)	Yes	1/7 embryos transferred (specifically from one thawed embryo)	-	1/1 clinical pregnancy	-
Kochhar and Ghosh, 2018 [80]	Case report	1 patient with complete globozoospermia	ICSI	1/11 (9.09%)	-	0/1 embryo transferred	-	-	-
		1 patient with complete globozoospermia	ICSI+AOA	7/18 (38.9%)	Yes	1/3 embryo transferred	-	1/1 clinical pregnancy	-
Koscinski et al, 2011 [101]	Case series	5 brothers with complete globozoospermia	ICSI	-	-	-	2/20 ICSI cycles	1/20 ICSI cycles	-

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Table 4. Continued 4

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Kuentz et al, 2013 [102]	Cross sectional	32 patients with complete globozoospermia and 2 with partial globozoospermia	ICSI	114/408	Yes 6/37 embryos transferred	6/37 embryos transferred	1/6 clinical pregnancies	5/6 clinical pregnancies	-
			ICSI+AOA with Ca^{++} ionophore	240/383	Yes 16/36 embryos transferred	13/36 embryos transferred	2/13 clinical pregnancies	11/13 clinical pregnancies	-
Kyono et al, 2009 [81]	Case report	1 patient with complete globozoospermia	ICSI+AOA with Ca^{++} ionophore	15/17	Yes	1/1 embryo transferred	-	1/1 clinical pregnancy	Good quality embryo (5BA)
Li et al, 2018 [103]	Case report	1 patient with combination of globozoospermia and acephalic spermatozoa and *DNAH6* mutation	ICSI	6/26	-	-	-	0	-
Li et al, 2021 [104]	Case reports	1 patient with total globozoospermia	ICSI	8/10	-	0/1 embryo transferred	-	-	
		1 patient with almost total globozoospermia	ICSI	6/6	-	1/1 embryo transferred	-	-	4 high quality blastocysts
Liu et al, 1995 [82]	Case series	7 patients with complete globozoospermia	ICSI	14/75	Yes 3/10 embryo transferred	2/10 embryo transferred	1/2 clinical pregnancy because was ectopic pregnancy	-	-
Liu et al, 2017 [105]	Case report	1 patient with complete globozoospermia	ICSI	28.6%	-	-	-	1	-
Modarres et al, 2016 [106]	Cross-sectional	27 patients with globozoospermia (24 total and 3 partial)	ICSI	-	Yes	6/27	1/6	3/6 clinical pregnancy	-
Moradan and Youse, 2014 [83]	Case report	1 patient with complete globozoospermia	ICSI	-	-	0/3 embryo transfers	-	0	-
		1 patient with partial globozoospermia	ICSI	-	-	0/3 embryo transfers	-	0	
Nardo et al, 2002 [84]	Case report	2 patients with total globozoospermia	ICSI	5/12	Yes	1/5 embryo transferred	-	1/1 clinical pregnancy	-

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Table 4. Continued 5

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Paci et al, 2017 [107]	Case series	4 patients with globozoospermia (3 complete and 1 partial)	ICSI	-	-	-	-	3 healthy boys in 2 patients	-
Pirrello et al, 2005 [108]	Case series	1 patient with globozoospermia	ICSI	0	-	-	-	-	-
Sahu et al, 2010 [85]	Case report	1 patient with complete globozoospermia	ICSI	3/9	Yes	1/2 embryo transferred	-	1/1 clinical pregnancy	One grade 1 embryo and one grade 2 embryo
Sermondade et al, 2011 [86]	Case report	1 patient with complete globozoospermia	IMSI	3/5	Yes	1/2 embryos transferred	-	1/1 clinical pregnancy	2 top quality embryos (blastomeres without any fragmentation)
			IMSI+AOA with Ca^{++} ionophore	4/6	-	-	-	-	-
Shang et al, 2019 [109]	Case series	9 patients with total globozoospermia	ICSI+AOA	50/70	-	-	-	7	-
Stone et al, 2000 [87]	Case report	1 patient with complete globozoospermia	ICSI	13/35	Yes	1/7 embryos transferred	-	1/1 clinical pregnancy	-
Tavalaee et al, 2016 [88]	Case series	12 patients with complete globozoospermia	ICSI+AOA with Ca^{++} ionophore	66/115	Yes	7/25 embryos transferred	2/7 clinical pregnancies	5/7 clinical pregnancies	-
Tavalaee et al, 2018 [89]	Case control	32 patients with complete globozoospermia and DPY19L2 deletion	ICSI+AOA	53.14±5.13	-	-	-	53.8% (14/26 embryo transferred)	-
		32 fertile controls	ICSI	87.64±2.38	-	-	-	-	-
Tejera et al, 2008 [110]	Case report	1 patient with complete globozoospermia	ICSI	5/14	-	-	-	-	Superior embryo quality after AOA
			ICSI+AOA with Ca^{++} ionophore	5/9	Yes	1/2 embryos transferred	-	1/1 clinical pregnancy	

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Table 4. Continued 6

Reference	Type of study	Population	Type of ART procedure	Fertilization rate (n of oocytes)	Biochemical pregnancy	Clinical pregnancy	Pregnancy loss	Live birth	Embryo quality
Tesarik et al, 2002 [90]	Case report	2 patients with complete globozoospermia	ICSI	0/9	-	-	-	-	Superior embryo quality in modified ICSI than ICSI+AOA
			ICSI+AOA with Ca^{++} ionophore	8/12	-	0/3 embryos transferred	-	-	
			Modified ICSI without AOA	9/14	-	1/3 embryos transferred	-	1/1 clinical pregnancy	
Trokoudes et al, 1995 [91]	Case report	1 patient with complete globozoospermia	ICSI	3/6	Yes	1/2 embryos transferred	-	1/1 clinical pregnancy	High quality embryos
Vozdova et al, 2014 [111]	Case report	1 patient with complete globozoospermia	ICSI	22/36	-	0/11 embryos transferred	-	-	High quality embryos
Yassine et al, 2015 [92]	Case series	9 patients with total globozoospermia	ICSI	17/139	-	-	-	2	10 embryos transferred but only 2 of high quality
Zeyneloglu et al, 2002 [93]	Case report	1 patient with complete globozoospermia and Y chromosome microdeletion	ICSI	4/13	Yes	2/4 embryos transferred	-	2/2 clinical pregnancies	-
Zhang et al, 2016 [94]	Case report	1 patient with complete globozoospermia	ICSI	0/11	-	-	-	-	-
		1 patient with partial globozoospermia	ICSI	4/11	Yes	1/2 embryos transferred	-	1/1 clinical pregnancies	-
Zhioua et al, 2011 [95]	Case series	6 patients with globozoospermia (both partial and complete)	ICSI	10/56	-	0/9 embryos transferred	-	-	-

ART: assisted reproductive technique, AGT: assisted gamete treatment, AOA: assisted oocyte activation, ICSI: intracytoplasmic sperm injection, IMSI: intracytoplasmic morphologically selected sperm injection, IVF: *in vitro* fertilization, OASCF: oocyte-activating sperm cytosolic factor, SPATA16: spermatogenesis-associated 16.

rate of *in vitro* fertilization (IVF) is much lower in patients with partial globozoospermia compared to controls, therefore suggesting that this technique should be avoided even when not all spermatozoa have round heads [71].

The association of ICSI with assisted oocyte activation (AOA), in most cases performed by adding calcium ionophore, significantly improves the mean fertilization rate (58.8%±23.7%) [59,64,66,74,79-81,88,90,100,109,110]. Furthermore, in a single case that reports a successful pregnancy in a patient with globozoospermia and *SPATA16* mutation, a very low fertilization rate (8.3%) was found, even with the use of AOA after ICSI [100]. Only one study compared conventional ICSI with intracytoplasmic morphologically selected sperm injection (IMSI) and found an improvement in fertilization rate when a careful morphological selection of spermatozoa was performed (37.5% *vs.* 11.1%) [97]. Two other studies compared IMSI with and without AOA and found no significant difference between the two procedures (55%±7.1% *vs.* 61%±7.1%) [75,86]. Only one case evaluated the effects of ICSI performed after hyaluronic acid sperm selection (HA-ICSI), reporting a fertilization rate of 66.6% [63]. Moreover, comparing this method with conventional ICSI, the authors found a higher fertilization rate in patients undergoing HA-ICSI [62]. Finally, one study on a patient with total globozoospermia evaluated hard activation ICSI with a fertilization rate of 22.6% [72].

As far as the quality of the transferred embryos, the few studies that have evaluated this aspect seem to highlight the lack of effect of globozoospermia on embryo quality [62-65,68,71,72,82,86,87,91-93,108,111]. Only one study showed low embryo quality in 9 patients with total globozoospermia [93]. Only one study found a superior embryo quality in patients who underwent ICSI plus AOA than those who underwent conventional ICSI [90]. Moreover, two studies that compared embryo quality between men with partial globozoospermia and control without the disease, found that the embryo quality seems to be unaffected in patients with partial globozoospermia [63,71] and, in one study, it seems higher in patients than in controls [63].

Patients with total globozoospermia who underwent ICSI had a very low clinical pregnancy rate (19.5%). The rate of live birth after clinical pregnancy is 63.6% and the miscarriage rate is 27.3%. At the time of publication of the respective studies, 9.1% pregnancies were still ongoing [60,61,64,68,74,77,78,80,82-85,87,91,93,98,104]. Considering the patients who underwent ICSI plus AOA, a higher clinical pregnancy rate (31.3%) can be observed, with a live birth rate of 86.7% and a miscarriage rate of 13.3% [63,66,74,79-81,88,90,110].

We were able to extract data on clinical pregnancy in patients with partial globozoospermia treated with ICSI from 4 studies, finding a clinical pregnancy rate of 46.2% on the total number of embryos transferred, with a live birth rate of 66.6% and abortion rate of 16.7%. One pregnancy was still ongoing (16.7%) at the time of the study writing [77,83,84,104]. Only one study compared the rates of clinical pregnancy, live birth, and miscarriage in patients with globozoospermia *versus* disease-free controls and found that they overlap [63]. Only two studies evaluated IMSI with only one clinical pregnancy from 9 transferred embryos resulting in a live birth [86,97]. In contrast, there are no extractable data on these outcomes for IMSI plus AOA.

4) Globozoospermia and offspring's health

Our search strategy did not allow us to find any specific study that evaluated as a primary outcome the health of offspring born to patients with globozoospermia. However, studies evaluating ICSI outcomes provide some insight into the offspring's health soon after birth. In particular, all children born from patients with globozoospermia seem to be healthy after birth. Only one study reported the voluntary termination of a pregnancy because of the presence of isochromosome 12 in the fetus [59], whereas in another, 1 of 2 children born from a patient with complete globozoospermia and *ZPBP* mutation had a cardiofaciocutaneous syndrome [48].

DISCUSSION

Globozoospermia is a rare syndrome accounting for about 0.1% of all causes of male infertility. It is probably due to the autosomal recessive transmission of mutations of genes involved in the acrosome biogenesis [112]. In this systematic review, we have examined the genes possibly implicated in this disease, finding that the main role is played by the *DPY19L2* gene encoding for a protein located in the inner nuclear membrane that contributes to the anchoring of the acrosome to the inner nuclear membrane. In the absence of DPY19L2, the inner nuclear membrane is separated

from the outer nuclear membrane, leading to the complete detachment of the acrosome [112,113]. Several mutations in this gene have been reported and the case herein reported has a never-described mutation ofthe *DPY19L2* gene that could cause globozoospermia.

In a variable proportion of patients with globozoospermia, *DPY19L2* gene mutations are not found. Therefore, several studies have been carried out in the attempt to identify mutations in other genes involved in acrosome biogenesis. These include *SPATA16* and *PICK1*. *SPATA16* is a highly conserved mammalian testis-specific protein localized in the Golgi apparatus, thus suggesting its role in acrosome biogenesis [99]. In mouse models, dysfunction in this protein is associated with infertility and impaired spermiogenesis [114]. In humans, the homozygous point mutation c.848G>A in exon 4 causes loss of the biological effect of the protein due to an inappropriate splicing of exon 4 [99]. Similarly, the deletion of exon 2 could alter the functional domain, resulting in altered SPATA16-mediated protein-to-protein interactions. According to Ghédir et al [39], this alteration is also associated with meiosis defects that explain the higher rate of double- or multiple-headed and multi-tailed spermatozoa in patients with this mutation compared to those with *DPY19L2* gene mutations.

PICK1 encodes for a 415 amino acid cytosolic protein that interacts with membrane proteins [44]. The *Pick1*-knockout mouse model showed the presence of infertility with a phenotype similar to that of human globozoospermia [115]. At the testicular level, the main regulator of PICK1 function is the islet cell autoantigen 1-like (ICA1L) protein that binds PICK1s by interfering with the formation of PICK-1 homodimers. Confirming this interaction, knockout mice for this protein present a phenotype very similar to that of PICK1 knockout mice [116].

SPACA1 can interact with ZPBP, to induce the attachment of acrosomal granules and on the acroplaxome, and also to actin-like protein 7A (ACTL7A) to attach the acrosome to the nucleus. The failure of SPACA1 to bind to ACTL7A reduces ACTL7A expression resulting in direct damage to the acroplaxome and tail, leading to a round head and a coiled tail. In turn, this results in globozoospermia [96].

ZPBP and *CCDC62* genes may also be involved, when mutated, in the pathogenesis of globozoospermia in humans [49] and in mice [117,118]. In mice, the absence of ZPBP1 protein alters the acrosome compaction, leading to its fragmentation and subsequent internalization in Sertoli cells [117]. Similarly, the CCDC62 protein is expressed at all stages of mice acrosome biogenesis, and its knock out results in development of infertility in mice. Furthermore, the interaction with the GOPC protein appears to be critical for its effects on acrosome biogenesis. Indeed, its absence in mice is associated with globozoospermia. However, to date, no mutations of this gene have been shown in patients with globozoospermia [118].

C2CD6 appears to be involved in acrosome biogenesis through interaction with *SPATA16* and *ZPBP*. C7orf61 and CCIN have also an acrosomal localization, and CCIN binding to actin could be involved in the transport of acrosomal vesicles from the Golgi apparatus to the apex of the sperm head during the acrosome biogenesis phase [48]. DNH17 protein is linked to infertility in mice [49]. Indeed, dyneins seem to play a role in Golgi transport and maintenance and thus in acrosome formation. Indeed, mutation of the dynein-coding *DNH6* is associated with sperm acephaly and globozoospermia [103]. Finally, *GGN* encodes for gametogenetin, a protein able to interact with several other proteins involved in spermatogenesis [31,49]. Among these, gametogenetin binding protein 1 (GGNBP1) seems to be involved in the biogenesis of the acrosome and therefore in the formation of round-headed spermatozoa without acrosome [119]. The knockout mouse model for GGN is not compatible with life and, therefore, no murine model allows us to test the direct effects of mutations of this gene [31].

Patients with globozoospermia are infertile because of the inability of their spermatozoa to bind the zona pellucida and penetrate the oocyte. Therefore, ICSI represents the only solution to achieve pregnancy. However, the fertilization rate after conventional ICSI turns out to be lower than normal, suggesting that in addition to the inability to penetrate the zona pellucida, other mechanisms are lacking in these patients [5]. Among these the lack of factors associated with oocyte activation present in the acrosome seems to play a fundamental role. In detail, those mainly evaluated are phospholipase C zeta (PLCζ), post-acrosomal sheath WW binding-domain protein (PAWP), and a truncated form of KIT (tr-Kit) [11,14]. Confirming the role of PLCζ and PAWP, a significant reduction in the expression of these two proteins in globozoospermic

patients compared with fertile men has been observed [11]. Moreover, PLCζ in localized the equatorial/post-acrosomal area of human spermatozoa and, in particular, in the perinuclear theca side, attached to the inner acrosomal membrane (IAM). The equatorial zone is the first area responsible for the fusion of the two gametes. At this level, the PLCζ would determine the initial increase in calcium levels essential for the process of fertilization. Furthermore, both IAM and the perinuclear theca remain after the acrosome reaction and consequently PLCζ is delivered inside the oocyte after the fusion of the two gametes [67]. Accordingly, the exogenous injection of mRNA encoding for PLCζ can induce calcium oscillations in the oocyte similar to those occurring during gamete fusion, confirming the fundamental role of this protein. The release of calcium within the oocyte then acts by modulating many essential processes involved in fertilization process [120,121]. In agreement when patients are selected based on the presence of oocyte-activating sperm cytosolic factor (OASCF) the fertilization rate with conventional ICSI in patients with OASCF is similar to the fertilization rate of patients without OASCF undergoing AOA [97]. Further evidence of the role of these factors is given by the higher fertilization rate of IMSI compared to ICSI. Although IMSI does not use factors that favor the activation of oocytes, equally the fertilization rate improves. This is because IMSI offers a more detailed morphological sperm examination, allowing the identification of acrosomal bud carrying cytosolic factors essential for oocyte activation. This evidence also explains why even by associating IMSI with AOA, the fertilization rate does not improve [86].

Although the fertilization rate improves significantly with the use of AOA, it is equally lower than the norm. Moreover, the success rate of ICSI in terms of clinical pregnancy rate is low also when fertilization improves with AOA. These findings suggest that other factors also intervene in decreasing the success rate of ICSI [89]. In this systematic review, we highlighted that patients with globozoospermia have a higher sperm aneuploidy rate than healthy controls. The latter is associated with lower pregnancy and implantation rates and to higher miscarriage rate after ICSI, due to the higher risk of developing embryos with chromosomal abnormalities [122]. In patients with *SPATA16* mutations, the rate of sperm aneuploidy seems to be even higher than in patients with a mutation of the *DPY19L2* gene. This finding can be explained by the meiosis defect that these patients have [39]. Furthermore, this might partly explain why the fertilization rate of these patients is remarkably low despite the use of ICSI plus AOA procedures [100].

Finally, DNA fragmentation may also play a role. Indeed, patients with globozoospermia have a higher sperm DNA fragmentation rate than normal men [56]. In turn, DNA damage negatively affects clinical pregnancy following IVF and/or ICSI treatment [123]. The genesis of this DNA damage could be imputed to the alteration of normal chromatin compaction processes. Indeed, murine studies have shown that the normal process of nuclear invasion by protamines, which is essential for the compaction of sperm DNA, does not occur in *Dpy19l2*-knockout mice [92]. This favors DNA damage and epigenetic changes that, in turn, hinder embryonic development [92].

This systematic review has some limitations. First, all included studies are of low quality because most of them are case reports. However, the rarity of the condition should also be taken into account. Thus, there is a lack of high-quality studies that have evaluated ICSI outcomes. Moreover, the available studies provide scanty information on the age or possible diseases of the female partners of globozoospermic patients. This could partly explain the considerable variability in terms of fertilization rate and other ICSI outcomes among studies. Finally, often the populations examined overlap between studies, which could explain the considerable variability in the rate of genetic mutations reported.

CONCLUSIONS

In conclusion, we herein reported a new mutation of the *DPY19L2* gene in a patient with globozoospermia. The associated systematic review allowed us to summarize the evidence on 1) the gene panel to be evaluated, 2) ICSI outcomes, and 3) the health of the offspring of patients with globozoospermia. Although there is not an increased risk for poor offspring health in patients with globozoospermia, only few studies have assessed this specific outcome and further studies are needed. According to our findings, the following recommendations on the management of patients with globozoospermia can be given:

We suggest that patients with globozoospermia

should be evaluated for mutations in the *DPY19L2*, *SPATA16*, *PICK1*, *GGN*, *SPACA1*, *ZPBP*, *CCDC62*, and *CCNB3* (weak recommendation, very low quality of evidence) (2, ØOOO).

We suggest ICSI with AOA or IMSI to patients with globozoospermia to improve the chance of success, since thy allows the selection of spermatozoa with an acrosomal bud (weak recommendation, very low quality of evidence) (2, ØOOO). We suggest conventional ICSI to patients with partial since their fertilization rate is similar to that of patients with other types of infertility (weak recommendation, low quality of evidence) (2, ØØOO).

We suggest investigating DNA fragmentation and sperm aneuploidy rate in patients with globozoospermia which can explain the lower clinical pregnancy rate seen in these patients compared with other infertile patients (weak recommendation, low quality of evidence) (2, ØØOO).

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: RC, AEC, AC. Data curation: AC, RAC, RC. Formal analysis: AC, RC. Methodology: AC, RAC. Project administration: RC, AEC. Supervision: RC, AEC, SLV. Validation: RAC, SLV. Visualization: RAC, SLV. Writing – original draft: AC. Writing – review & editing: RC, AEC, RAC, SLV.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.220020.

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