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Assisted Oocyte Activation following Intracytoplasmic Sperm Injection: A Sensible Option for Infertile Couples with Severe Teratozoospermia

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Abstract

The intracytoplasmic sperm injection (ICSI) has significantly improved male factor infertility treatment; however, complete fertilization failure still occurs in 1-5% of ICSI treatment cycles mainly due to oocyte activation failure. It is estimated that around 40-70% of oocyte activation failure is associated with sperm factors after ICSI. Assisted oocyte activation (AOA) as an effective approach to avoid total fertilization failure (TFF) has been proposed following ICSI. In the literature, several procedures have been described to overcome failed oocyte activation. These include mechanical, electrical, or chemical stimuli initiating artificial Ca^{2+} rises in the cytoplasm of oocytes. AOA in couples with previous failed fertilization and those with globozoospermia has resulted in varying degrees of success. The aim of this review is to examine the available literature on AOA in teratozoospermic men undergoing ICSI-AOA and determine whether the ICSI-AOA should be considered as an adjunct fertility procedure for these patients.

Keywords: Assisted Oocyte Activation, Failed Fertilization, Intracytoplasmic Sperm Injection, Pregnancy, Teratozoospermia

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Introduction

The diagnosis of male infertility is commonly based on semen analysis, however, in some cases male fertility assessment is not possible due to the descriptive nature of semen analysis. One of the most common reasons of male infertility is teratozoospermia (1). This term refers to semen samples in which the percentage of normal sperm morphology is below the threshold value defined by the World Health Organization (WHO). This threshold has varied significantly (50 to 4%) from the first to the latest edition of WHO since 1980 to 2021 (2). Teratozoospermia is associated with a wide range of abnormalities in the sperm head, neck, mid-piece, principle, and tail regions (3). Chemes et al. (4, 5) suggested that there are a number of ultrastructural abnormalities in sperm that cannot be assessed by microscopic evaluation of sperm morphology and so far have not been described by the WHO. As such, the latest edition of WHO (2021) states that a number of individuals with normal ejaculate analysis, could have sperm with structural abnormalities in the acrosome region and acrosome reaction affecting the ability of these sperm to penetrate and activate the oocytes (6). In some semen samples there are certain sperm abnormal phenotypes which are dominant like: round-head (globozoospermia), large-head (macrozoospermia), acephalic, pear head shape, amorphic, and multiple morphological abnormalities of the flagella (MMAF) (7). It is now well established that the treatment strategy for this type of infertility is intracytoplasmic sperm injection (ICSI). Although ICSI is considered as the sole treatment approach for severe teratozoospermia, the fertilization and ICSI success rate are limited in patients with some of the above abnormal dominate phenotypes, like globozoospermia or cases with small head (8-11). To improve ICSI success rate, ICSI along with assisted oocyte activation (AOA) has been proposed (12, 13). It has been shown that AOA could increase ICSI success rate in patients with globozoospermia or individuals with failed fertilization in previous *in vitro* fertilization (IVF) cycles (14), however, limited attention has been paid to AOA due to sole teratozoospermia.

The low fertilization rate following ICSI in severe teratozoospermia appears to be related to the inability

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of such sperm to induce oocyte activation (OA) (10, 15). Oocyte activation is induced upon release of sperm-borne oocyte activation factor (SOAF) from equatorial or post-acrosomal sheath (PAS) region of sperm into oocyte. Numerous factors have been reported to play this role but it is now evident that a sperm-specific phospholipase C zeta (PLCζ) acts as main SOAF and other factors may have complementary role in the activation process. After the release of PLCζ from sperm into the oocyte, it hydrolyzes phosphatidylinositol 4, 5-bisphosphate (PIP2) into inositol-1,4,5-triphosphate (IP3) and diacylglycerol (DAG). IP3 stimulates the release of calcium from the endoplasmic reticulum into the oocyte cytoplasm and induces calcium oscillations inducing oocyte activation and meiotic resumption (15). Heytens et al. (16), and other investigators (17) have demonstrated the expression of PLCζ in the sperm PAS and its key role during fertilization and, stated that male infertility is associated with the mutant forms of PLCζ. In addition, sperm with abnormal morphology or sperm with small or absent acrosome (globozoospermia) are unable to penetrate the zona pellucida and possess a lower capacity for the oocyte activation (18-20). This may be associated with absence or low expression of PLCζ and failed oocyte activation. Several studies displayed a functional correlation between the expression of PLCζ in sperm with ability to trigger calcium oscillations and oocyte activation (21, 22).

Concerns regarding the health of children born through ICSI-AOA was raised (23). AOA is not a routinely used technique in most IVF centers because of its safety concerns, and there is a need for large prospective studies to examine its safety. A recent meta-analysis considering 4 studies show that AOA does not significantly increase the rate of major anomalies in children born through ICSI-AOA. In addition, the neonatal and neurodevelopmental outcomes of children aged ≥ 3 years were within the expected ranges (24). However, a plea for caution not to utilize AOA in cases where AOA is not necessary remains (23). Despite such a plea, current literature indicate that AOA is being implemented for couples with different infertility categories referred for treatment (13). This review aims to describe the clinical outcome of teratozoospermic men who underwent ICSI-AOA and determine whether the ICSI-AOA should be considered as a suitable option for these infertile couples.

Search strategy

A computerized literature search was conducted for studies in English language in PubMed, Science Direct and Google Scholar between 2006 and 2022. We aimed to identify all relevant studies that compared fertilization and pregnancy outcome, and health of children conceived by ICSI-AOA compared with conventional ICSI. The terms teratozoospermia, intracytoplasmic sperm injection, assisted oocyte activation, fertilization rate, congenital abnormalities, and birth defects were used as keywords to extract the relevant literature. Details on the strategy of search as well inclusion and exclusion criteria are shown in Table 1. Globozoospermia is excluded since using AOA for these couples has been well-established.

Table 1: Search criteria and eligibility

Databases	**PubMed, Science Direct, and Google Scholar**
Keywords	Teratozoospermia, Intracytoplasmic sperm injection, Assisted oocyte activation, Fertilization rate, Congenital abnormalities, and Birth defects
Years	2006-2022
Outcomes	The ICSI-AOA technique as a recommended option for teratozoospermic men
Language	English
Type of study design	- Prospective pilot study - Laboratory study - Case report study - Prospective, randomized, unblinded clinical study - Pilot historical cohort study - Prospective randomized sibling oocyte study - Retrospective study - Original study
Inclusion criteria	- Studies on teratozoospermia (abnormal morphology <4 %) - The exposure of oocytes to SrCl2, Ionomycin; Electrical; Calcium ionophore - The outcome of interest was: fertilization, pregnancy, and health of children born through ICSI-AOA in humans - Comparison of ICSI-AOA to conventional ICSI
Exclusion criteria	- Studies on globozoospermia - Studies on other severe forms of teratozoospermia such as acephalic sperm or macrocephalic sample - Studies without full data - Poster studies - Studies with inappropriate comparison group or without control subjects

AOA; Assisted oocyte activation and ICSI; Intracytoplasmic sperm injection.

Intracytoplasmic sperm injection with assisted oocyte activation

ICSI is the most effective tool in assisted reproduction technology (ART) with high fertilization success, however total fertilization failure (TFF) following ICSI is still occurs in 1% to 5% of ICSI cycles in Europe and the United States (14, 25). According to the literature, TFF following ICSI is defined as the absence of male and female pronuclei in all oocytes injected during an ICSI cycle. TFF is strongly depended on the number of mature oocytes (MII) and in most cases, there is an inverse relationship between TFF and total number of oocytes available for ICSI. Sun and Yeh (14) reported 2.14% TFF in couples with 3 or more MII oocytes while they found 17.4% in couples with only 1 or 2 MII oocytes. TFF happens owing to technical problems, defects in the oocytes, or inability of sperm to induce oocyte activation (24). Technical errors were reported in almost 10% of couples with failed fertilization due to the sperm DNA that remains outside of the oocyte cytoplasm. It seems that in majority of the cases, oocyte activation failure (14) is considered as the main reason for total or partial failed fertilization.

As stated above, the main cause of failed fertilization after ICSI is "oocyte activation failure". Various mechanical, electrical, and chemical procedures have been used to assist oocyte activation (26). Among these methods, chemical oocyte activation using different materials such as ethanol, ionomycin and A23187 has been the most frequently applied procedure (27, 28). Table 2 shows information of 10 original published papers on AOA following ICSI in couples with teratozoospermia using different chemicals such as calcium ionophore, neomycin, and strontium chloride ($SrCl_2$) to induce calcium oscillation.

Table 2: Summary of the 10 papers to investigate the application of AOA treatment after ICSI in couples with teratozoospermia male factor

No.	Authors (Reference)	Type of study	Type of oocyte	Type of ART	Chemical	Cases (No.)	Age (Y)
1	Moaz et al. (9)	Prospective pilot	M-II	ICSI	Ionomycin	ST n=56	Female: 22- 37 Male: Not reported
2	Nasr-Esfahani et al. (10)	Laboratory	M-II (Sibling oocytes)	ICSI	Ionomycin	ST n=87	Female: 18-40 Male: 19-45
3	Eftekhar et al. (28)	Prospective, randomized, unblinded clinical	M-II	ICSI	Calcium ionophore	TT n=38	Female: <40 Male: ≤40
4	Mansour et al. (29)	Prospective randomized	M-II	ICSI	Electrical	SOAT n=241	Female: <40 Male: Not reported
5	Nasr-Esfahani et al. (30)	Laboratory	M-II (Sibling oocytes)	ICSI	Ionomycin	ST n=8	Female: <35 Male: <40
6	Deemeh et al. (31)	Pilot historical cohort	M-II	ICSI	Ionomycin	ST n=681	Female: <36 Male: ≤40
7	Kim et al. (32)	Case report	M-II	ICSI	Calcium ionophore	MOT n=1	Female: 32 Male: 33
8	Aydinuraz et al. (33)	Prospective randomized sibling oocyte	M-II (Sibling oocytes)	IMSI	Calcium ionophore	TT n=21	Female: <35 Male: <35
9	Norozi-Hafshejani et al. (34)	Prospective randomized sibling oocyte	M-II (Sibling oocytes)	ICSI	Ionomycin/ $SrCl_2$	ST n=105	Female: <35 Male: <40
10	Li et al. (35)	Retrospective	M-II	ICSI	Ionomycin	SOAT n=194	Female: <40 Male: ≤45

AOA; Assisted oocyte activation, ICSI; Intracytoplasmic sperm injection, M-II; Metaphase II, ART; Assisted reproductive technology, ST; Severe teratozoospermia, TT; Teratozoospermia, SOAT; Severe oligoasthenoteratozoospermia, and MOT; Moderate oligoteratozoospermia.

ICSI-AOA and fertilization outcomes

From the 10 studies, information regarding fertilization and cleavage rates and development to day 3 or blastocyst stage were available in 7 papers (Table 3). A significant increase in fertilization rate was reported in four studies (9, 10, 29, 30), and significantly improved cleavage rate was reported in one study (10), also, a significant difference in the percentage of high quality embryos was observed in the Aydinuraz et al. (33) study. A recent study demonstrated that mean number of high quality blastocysts significantly increased after ICSI-AOA in couples with unexplained infertility, OAT, PCOS and couples with both male and female factors compared with their previous cycles (13).

The application of Ca^{2+} in oocyte activation has been investigated in depth. For years, the ICSI-AOA has been successfully used in cases of severe male infertility and resulted in increased fertilization rate and clinical outcome (9, 10, 36, 37). Swann et al. (38) observed the induction of calcium oscillations after microinjection of PLCζ cRNA into oocytes of couples with history of failed fertilization. Recently, a review study by Sun and Yeh (14) has emphasized that one main reason for total failed fertilization in animal and human oocytes could be associated to abnormal calcium oscillations post- fertilization.

ICSI-AOA and pregnancy outcomes

Table 4 shows implantation and pregnancy outcomes including biochemical pregnancy, clinical pregnancy, miscarriage and ongoing pregnancy rates in ICSI-AOA and ICSI groups. Some studies revealed that there was no significant difference between the ICSI-AOA and ICSI pregnancy outcomes (28-31, 33). However, the ICSI-AOA treatment can improve fertilization rate, and potentially provide more available embryos, which in turn, may increase cumulative pregnancy rate. When oocytes are activated and fertilized, their subsequent development depends on several factors including chromatin and chromosomal (ploidy status) integrity and may not be influenced by AOA. Overall, literature suggest that the latter two parameters are lower in severe teratozoospermia (39) and published studies have shown that sperm DNA fragmentation is associated with abnormal morphology (40, 41).

Table 3: Overview of the effect of ICSI-AOA in fertilization outcomes in the patients with teratozoospermia male factor

No.	Authors (Reference)	Male factor	Fertilization rate (%)[a]			Cleavage rate (%)[b]			High quality embryo rate (%)[c]		
			ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value
1	Moaz et al. (9)	ST (n=56) A=amorphous head B=tapered head C=bent neck	36.7 39.3 49.4	82.7 81.7 48.2	0.0008 0.005 NS	51.5 47.8 3.6	51.9 50.4 42.5	NS NS NS	57.6 65.2 61.5	58.0 64.1 62.5	NS NS NS
2	Nasr-Esfahani et al. (10)	ST (n=87)	52.73	66.79	0.001	49.95	74.77	0.001	67.16	67.9 9	NS
3	Eftekhar et al. (28)	TT (n=38)	84.4	95.33	NS	89.56	87.74	NS	44.4	35.3	NS
4	Mansour et al. (29)	SOAT (n=241)	60	68	P<0.0001	NR	NR	NR	NR	NR	NR
5	Nasr-Esfahani et al. (30)	M-II (Sibling oocytes) ST (n=12)	64.00	91.75	<0.05	NR	NR	NR	NR	NR	NR
		M-II NSM (n=41) ST (n=8)	76.16	70.14	NS	NR	NR	NR	NR	NR	NR
6	Aydinuraz et al. (33)	TT (n=21)	73.2	82.5	NS	91.5	91.3	NS	53.5	35	0.024
7	Norozi-Hafshejani et al. (34)	ST (n=105)	68.58*	Ionomycin: 65.23 $SrCl_2$: 49.65	NS 0.005	NR	NR	NR	16.70*	Ionomycin: 20.65 $SrCl_2$: 29.9	NS NS

AOA; Assisted oocyte activation, ICSI; Intracytoplasmic sperm injection, NS; Not significant, NR; Not report, ST; Severe teratozoospermia, SOAT; Severe oligoasthenoteratozoospermia, TT; Teratozoospermia, NSM; Percentage of sperm with normal morphology higher than 4% in semen, [a]; Defined as the ratio of fertilized oocytes/ the total number of survived injected metaphase II (MII) oocytes×100, [b]; Defined as the total of cleaved embryos on day 3/number of zygotes×100, [c]; Defined as the number of top quality embryos on day 3/the number of normally fertilized oocytes×100, and *; The external control group with routine ICSI/AOA procedure using Ionomycin.

Table 4: Overview of the effect of ICSI-AOA on pregnancy outcomes in the cases with teratozoospermia male factor

No.	Authors (Reference)	Implantation rate (%)[a]			Chemical pregnancy (%)[b]			Clinical pregnancy (%)[c]			Abortion (NO. or %)[d]			Ongoing pregnancy (%)[e]		
		ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value	ICSI	ICSI-AOA	P value
1	Eftekhar et al. (28)	7.4	17.6	NS	16.7	47.1	0.07	16.7	41.2	NS	0	11.8	NS	100	85.7	NS
2	Mansour et al. (29)	NR	NR	NR	NR	NR	NR	48	44	NR	9	20	NR	NR	NR	NR
3	Nasr-Esfahani et al. (30)	21* 21	18** 9.1	NS 0.042	NR	NR	NR	48* 48	50** 25	NS NS	NR	NR	NR	NR	NR	NR
4	Deemeh et al. (31)	NR	NR	NR	NR	NR	NR	33.0	43.2	NS	13.4	13.0	NS	NR	NR	NR
5	Aydinuraz et al. (33)	40.0	33.3	NS	0	0	-	40.0	33.3	NS	10	0	NS	30.0	33.3	NS

AOA; Assisted oocyte activation, ICSI; Intracytoplasmic sperm injection, NS; Not significant, NR; Not report, βhCG; Beta human chorionic gonadotropin, [a]; Defined as the fraction of gestational sac(s) to the number of embryos transferred, [b]; Defined as the serum βhCG ≥25 IU/L after 2 weeks of embryo transfer, [c]; Defined as the presence of a gestational sac with heart beat on vaginal or abdominal ultrasound at 3-5 weeks after embryo transfer, [d]; Defined as pregnancy losses before 20 weeks of gestation, [e]; Defined as progression beyond 12 weeks of gestation, *; This control ICSI group included couples whose sperm had normal morphology, and **; The ICSI- AOA groups included couples with teratozoospermia and in sibling oocytes at least 50% of inseminated oocytes were artificially activated by exposure to Ionomycin.

The improvements in embryo development and implantation rates could have resulted from Ca^{2+} oscillation restoration to physiological or supra-physiological status (42), that influences events necessary for mammalian embryonic development both early events such as oocyte activation (43, 44), and late events including post-implantation developmental competency (45). Researchers have revealed that lack of Ca^{2+} signaling could alter preimplantation development, blastocyst quality, and profile of gene expression (46, 47). In addition to implantation and post implantation development, long-term fetal morphology and variation of offspring weight are believed to be affected by changed Ca^{2+} signaling patterns in mouse embryos (45). In mammals sperm-induced Ca^{2+} oscillations, which are vital for oocyte activation, continue for several hours until pronucleus formation. Therefore, proper regulation of Ca^{2+} signaling following oocyte activation is essential to achieve developmentally competent embryos, and healthy offspring. Lv et al. (13) applied ICSI-AOA in 796 couples with low or failed fertilization, poor embryo quality, and couples with male and/or female infertility, and compared clinical outcomes with their previous cycle. They concluded that AOA could significantly improve implantation, and clinical pregnancy. In addition, live birth rate significantly improved in the aforementioned groups except in women with primary ovarian insufficiency. The miscarriage rate significantly reduced in couples with OAT, PCOS, and unexplained infertility following ICSI-AOA cycles compared to their previous cycle. Subsequent, Table 5 is revealed a summary of the conclusions of the 10 papers that investigated the application of the ICSI-AOA in couples with teratozoospermia male factor.

Table 5: Summary of the conclusions of the 10 papers that were investigated the application of the ICSI-AOA in couples with teratozoospermia male factor

No.	Authors (Reference)	Conclusions
1	Moaz et al. (9)	The ICSI-AOA in cases with 100% sperm abnormal morphology may increase fertilization rate in some sperm morphological abnormalities (amorphous head and tapered head) but not in others sperm morphological (bent neck). However, there was no significant effect on early cleavage or number of good embryos in all subgroups.
2	Nasr-Esfahani et al. (10)	The ICSI-AOA in cases with severe teratozoospermia may improve fertilization and cleavage rates, which in turn, affect the implantation and pregnancy rate.
3	Eftekhar et al. (28)	The ICSI-AOA in cases with teratoozoospermia resulted in a significant increase in the fertilization and cleavage rates, and an insignificant improvement in the implantation and pregnancy rates.
4	Mansour et al. (29)	The ICSI-AOA (oocyte electroactivation) in cases of severe oligoasthenospermia or azoospermia with 100% abnormal forms or zero motility significantly improved the fertilization rate.
5	Nasr-Esfahani et al. (30)	Pregnancy rate was insignificantly higher in ICSI and ICSI/ ICSI-AOA group compared to ICSI-AOA; however, a significant difference was obtained for implantation rates between the ICSI and ICSI-AOA groups, and also the fertilization rate is improved by AOA.
6	Deemeh et al. (31)	There is no difference in preterm delivery, lower birth weight, NICU hospitalization, abnormal behavior according to age, abnormal growth rate, and major birth defects in the ICSI-AOA cases compared to the ICSI cases.
7	Kim et al. (32)	The ICSI-AOA in cases with oligoteratozoospermia resulted in a clinical pregnancy and delivery.
8	Aydinuraz et al. (33)	The AOA-IMSI in teratozoospermic cases did not improve the fertilization rate and may reduce the ability of successfully fertilized oocytes to develop into top-quality embryos.
9	Norozi-Hafshejani et al. (34)	The ICSI-AOA in cases with 99–100% abnormal sperm morphology may be more in quality embryos.
10	Li et al. (35)	The ICSI-AOA in cases with severe oligoasthenoteratozoospermia did not adversely affect pregnancy and neonatal outcomes.

AOA; Assisted oocyte activation and ICSI; Intracytoplasmic sperm injection.

Safety of ICSI-AOA

A major concern regarding AOA procedure is its safety. However, reported data indicates that AOA did not result in birth defects. Deemeh et al. (31) have reported that ICSI-AOA has not imposed a greater risk on the physical and mental health of 79 children born through ICSI-AOA. In this retrospective cohort study, no difference was observed on structural malformations and chromosomal aberrations, malformation (heart, urogenital, and limb), birth weight, and the gestational week at the time of delivery in 83 babies born after ICSI-AOA as compared to babies born from ICSI alone (48). Moreover, one study included a cohort of 38 babies who were delivered following ICSI-AOA, and no congenital birth defects were detected (37). In addition, Vanden Meerschaut et al. (49) reported normal neurodevelopmental, intelligence, language, and social communication features in children born (ages 3-10 years) following the ICSI-AOA. Li et al (35). observed no significant differences between babies born in couples undergoing ICSI and ICSI-AOA in regards to birth weight, gestational age, sex, and preterm birth characteristics. Besides, a meta-analysis included 5 studies revealed that there is not enough evidence of the prevalence of chromosomal and non-chromosomal aberrations in children born following ICSI-AOA as compared to ICSI, and the risk of birth abnormality may be related to the ICSI methods or an primary male/female factor than AOA (50).

To ensure the safety of the AOA technique, in addition to health of children born through ICSI-AOA, researchers should consider the effect of AOA on gene expression profile. In this regard, a study showed that the gene expression profile following ICSI-AOA was similar to IVF and ICSI alone (51). A recent study showed that gene expression profiles from good quality blastocysts derived from ICSI-AOA using PLCζ-null-sperm and ionomycin or strontium chloride or human recombinant PLCζ or and/or TPEN, did not differ with gene expression profiles of good quality blastocysts derived from ICSI alone (52) , however, in this study comparison with IVF embryos was not carried out. Unlike these studies, a recent study assessed global patterns of gene expression in mouse blastocysts derived from ICSI-AOA compared to ICSI, and observed AOA could affect imprinted gene *Igf2r* regulated by the imprinted *Airn* lncRNA. However, more studies are needed to investigate the impact of this technique on the health of the next generation, especially in humans (53). In addition, chromosomal investigation using fluorescence in situ hybridization (FISH) has revealed that embryos resulting from ICSI-AOA have the normal chromosomal number (54).

Conclusion

To the best of our knowledge, this review is the first to include published studies on ICSI-AOA in infertile couples with teratozoospermia. We conclude that couples with severe teratozoospermia can benefit from ICSI-AOA in terms of higher fertilization rate, which in turn increases the number of available embryos and may improve the implantation and pregnancy rates. However existing controversy in the literature on the effect of AOA on fertilization rate may have resulted from case selection, limited sample size, and the type of chemical agents used to induce AOA. Therefore, prospective, randomized clinical trials are needed to address these ambiguities. In addition, published studies and meta-analysis suggest no enhanced risk of pregnancy and neonatal abnormality after ICSI-AOA, and AOA does not appear to inflict a higher risk of major birth defects and malformation. Therefore, based on these studies one may recommend that couples with teratozoospermia may benefit from AOA, but until the safety of the procedure is validated at an international scientific community, it is sensible to use ICSI-AOA mainly for those patients with history of TFF or those with few numbers of oocytes available for ICSI.

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Authors' Contributions

M.T., M.H.N.-E, N.N.; Collected and assessed papers, and wrote the manuscript. M.H.N.-E., N.E.; Critically reviewed the final draft. All authors read and approved the final manuscript.

References

1. Menkveld R. Clinical significance of the low normal sperm morphology value as proposed in the fifth edition of the WHO Laboratory Manual for the Examination and Processing of Human Semen. Asian J Androl. 2010; 12(1): 47-58.
2. Wang C, Mbizvo M, Festin MP, Björndahl L, Toskin I. Evolution of the WHO "Semen" processing manual from the first (1980) to the sixth edition (2021). Fertil Steril. 2022; 117(2): 237-245.
3. World Health Organization. WHO laboratory manual for the examination and processing of human semen. 6th ed. World Health Organization; 2021; 276.
4. Chemes HE, Rawe VY. Sperm pathology: a step beyond descriptive morphology. Origin, characterization and fertility potential of abnormal sperm phenotypes in infertile men. Hum Reprod Update. 2003; 9(5): 405-428.
5. Chemes HE, Alvarez Sedo C. Tales of the tail and sperm head aches: changing concepts on the prognostic significance of sperm pathologies affecting the head, neck and tail. Asian J Androl. 2012; 14(1): 14-23.
6. Xu F, Guo G, Zhu W, Fan L. Human sperm acrosome function assays are predictive of fertilization rate in vitro: a retrospective cohort study and meta-analysis. Reprod Biol Endocrinol. 2018; 16(1): 1-29.
7. Coutton C, Escoffier J, Martinez G, Arnoult C, Ray PF. Teratozoospermia: spotlight on the main genetic actors in the human. Hum Reprod Update. 2015; 21(4): 455-485.
8. Zahiri Z, Ghasemian F. Is it necessary to focus on morphologically normal acrosome of sperm during intracytoplasmic sperm injection? Indian J Med Res. 2019; 150(5): 477-485.
9. Moaz MN, Khattab S, Foutouh IA, Mohsen EA. Chemical activation of oocytes in different types of sperm abnormalities in cases of low or failed fertilization after ICSI: a prospective pilot study. Reprod Biomed Online. 2006; 13(6): 791-794.
10. Nasr-Esfahani MH, Razavi S, Javdan Z, Tavalaee M. Artificial oocyte

activation in severe teratozoospermia undergoing intracytoplasmic sperm injection. Fertil Steril. 2008; 90(6): 2231-2237.
11. Tavalaee M, Nomikos M, Lai FA, Nasr-Esfahani MH. Expression of sperm PLCζ and clinical outcomes of ICSI-AOA in men affected by globozoospermia due to DPY19L2 deletion. Reprod Biomed Online. 2018; 36(3): 348-355.
12. Sfontouris IA, Nastri CO, Lima MLS, Tahmasbpourmarzouni E, Raine-Fenning N, Martins WP. Artificial oocyte activation to improve reproductive outcomes in women with previous fertilization failure: a systematic review and meta-analysis of RCTs. Hum Reprod. 2015; 30(8): 1831-1841.
13. Lv M, Zhang D, He X, Chen B, Li Q, Ding D, et al. Artificial oocyte activation to improve reproductive outcomes in couples with various causes of infertility: a retrospective cohort study. Reprod Biomed Online. 2020; 40(4): 501-509.
14. Sun B, Yeh J. Calcium oscillatory patterns and oocyte activation during fertilization: a possible mechanism for total fertilization failure (TFF) in human in vitro fertilization? Reprod Sci. 2021; 28(3): 639-648.
15. Zafar MI, Lu S, Li H. Sperm-oocyte interplay: an overview of spermatozoon's role in oocyte activation and current perspectives in diagnosis and fertility treatment. Cell Biosci. 2021; 11(1): 4.
16. Heytens E, Parrington J, Coward K, Young C, Lambrecht S, Yoon SY, et al. Reduced amounts and abnormal forms of phospholipase C zeta (PLCζ) in spermatozoa from infertile men. Hum Reprod. 2009; 24(10): 2417-2428.
17. Grasa P, Coward K, Young C, Parrington J. The pattern of localization of the putative oocyte activation factor, phospholipase Cζ, in uncapacitated, capacitated, and ionophore-treated human spermatozoa. Hum Reprod. 2008; 23(11): 2513-2522.
18. Kimura Y, Yanagimachi R, Kuretake S, Bortkiewicz H, Perry A,Yanagimachi H. Analysis of mouse oocyte activation suggests the involvement of sperm perinuclear material. Biol Reprod. 1998; 58(6): 1407-1415.
19. Battaglia DE, Koehler JK, Klein NA, Tucker MJ. Failure of oocyte activation after intracytoplasmic sperm injection using round-headed sperm. Fertil Steril. 1997; 68(1): 118-122.
20. Stone S, O'Mahony F, Khalaf Y, Taylor A, Braude P. A normal livebirth after intracytoplasmic sperm injection for globozoospermia without assisted oocyte activation: case report. Hum Reprod. 2000; 15(1): 139-141.
21. Escoffier J, Lee HC, Yassine S, Zouari R, Martinez G, Karaouzène T, et al. Homozygous mutation of PLCZ1 leads to defective human oocyte activation and infertility that is not rescued by the WW-binding protein PAWP. Hum Mol Genet. 2016; 25(5): 878-891.
22. Cox LJ, Larman M, Saunders C, Hashimoto K, Swann K, Lai F. Sperm phospholipase Czeta from humans and cynomolgus monkeys triggers Ca^{2+} oscillations, activation and development of mouse oocytes. Reproduction. 2002; 124(5): 611-623.
23. van Blerkom J, Cohen J, Johnson M. A plea for caution and more research in the 'experimental'use of ionophores in ICSI. Reprod Biomed Online. 2015; 30(4): 323-324.
24. Meerschaut FV, Nikiforaki D, Heindryckx B, De Sutter P. Assisted oocyte activation following ICSI fertilization failure. Reprod Biomed Online. 2014; 28(5): 560-571.
25. Shinar S, Almog B, Levin I, Shwartz T, Amit A, Hasson J. Total fertilization failure in intra-cytoplasmic sperm injection cycles – classification and management. Gynecol Endocrinol. 2014; 30(8): 593-596.
26. Kashir J, Ganesh D, Jones C, Coward K. Oocyte activation deficiency and assisted oocyte activation: mechanisms, obstacles and prospects for clinical application. Hum Reprod Open. 2022; 2022(2): hoac003.
27. Nasr-Esfahani MH, Deemeh MR, Tavalaee M. Artificial oocyte activation and intracytoplasmic sperm injection. Fertil Steril. 2010; 94(2): 520-526.
28. Eftekhar M, Janati S, Rahsepar M, Aflatoonian A. Effect of oocyte activation with calcium ionophore on ICSI outcomes in teratospermia: a randomized clinical trial. Iran J Reprod Med. 2013; 11(11): 875.
29. Mansour R, Fahmy I, Tawab N A, Kamal A, El-Demery Y, Aboulghar M, et al. Electrical activation of oocytes after intracytoplasmic sperm injection: a controlled randomized study. Fertil Steril. 2009; 91(1): 133-139.
30. Nasr-Esfahani MH, Tavalaee M, Reza Deemeh M, Arbabian M, Parrington J. Can assessment of total acrosin activity help predict failed or low fertilization rate ICSI for implementation of artificial oocyte activation? The Open Andrology Journal. 2010; 2(1): 19-26.
31. Deemeh MR, Tavalaee M, Nasr-Esfahani MH. Health of children born through artificial oocyte activation. Reprod Sci. 2015; 22(3): 322-328.
32. Kim JW, Yang SH, Yoon SH, Kim SD, Jung JH, Lim JH. Successful pregnancy and delivery after ICSI with artificial oocyte activation by calcium ionophore in in-vitro matured oocytes: a case report. Reprod Biomed Online. 2015; 30(4): 373-377.
33. Aydinuraz B, Dirican EK, Olgan S, Aksunger O, Erturk OK. Artificial oocyte activation after intracytoplasmic morphologically selected sperm injection: a prospective randomized sibling oocyte study. Hum Fertil (Camb). 2016; 19(4): 282-288.
34. Norozi-Hafshejani M, Tavalaee M, Azadi L, Bahadorani M, Nasr-Esfahani MH. Effects of assisted oocyte activation with calcium-ionophore and strontium chloride on in vitro ICSI outcomes. Iran J Basic Med Sci. 2018; 21(11): 1109.
35. Li B, Zhou Y, Yan Z, Li M, Xue S, Cai R, et al. Pregnancy and neonatal outcomes of artificial oocyte activation in patients undergoing frozen-thawed embryo transfer: a 6-year population-based retrospective study. Arch Gynecol Obstet. 2019; 300(4): 1083-1092.
36. Borges Jr E, Braga DPdAF, de Sousa Bonetti TC, Iaconelli Jr A, Franco Jr JG. Artificial oocyte activation with calcium ionophore A23187 in intracytoplasmic sperm injection cycles using surgically retrieved spermatozoa. Fertil Steril. 2009; 92(1): 131-136.
37. Yoon HJ, Bae IH, Kim HJ, Jang JM, Hur YS, Kim HK, et al. Analysis of clinical outcomes with respect to spermatozoan origin after artificial oocyte activation with a calcium ionophore. J Assist Reprod Genet. 2013; 30(12): 1569-1575.
38. Swann K, Windsor S, Campbell K, Elgmati K, Nomikos M, Zernicka-Goetz M, et al. Phospholipase C-ζ-induced Ca^{2+} oscillations cause coincident cytoplasmic movements in human oocytes that failed to fertilize after intracytoplasmic sperm injection. Fertil Steril. 2012; 97(3): 742-747.
39. Fesahat F, Henkel R, Agarwal A. Globozoospermia syndrome: an update. Andrologia. 2020; 52(2): e13459.
40. Ferrigno A, Ruvolo G, Capra G, Serra N, Bosco L. Correlation between the DNA fragmentation index (DFI) and sperm morphology of infertile patients. J Assist Reprod Genet. 2021; 38(4): 979-986.
41. Ammar O, Tekeya O, Hannachi I, Sallem A, Haouas Z, Mehdi M. Increased Sperm DNA fragmentation in infertile men with varicocele: relationship with apoptosis, seminal oxidative stress, and spermatic parameters. Reprod Sci. 2021; 28(3): 909-919.
42. Fawzy M, Emad M, Mahran A, Sabry M, Fetih AN, Abdelghafar H, et al. Artificial oocyte activation with SrCl2 or calcimycin after ICSI improves clinical and embryological outcomes compared with ICSI alone: results of a randomized clinical trial. Hum Reprod. 2018; 33(9): 1636-1644.
43. Ducibella T, Fissore R. The roles of Ca^{2+}, downstream protein kinases, and oscillatory signaling in regulating fertilization and the activation of development. Dev Biol. 2008; 315(2): 257-279.
44. Ducibella T, Huneau D, Angelichio E, Xu Z, Schultz RM, Kopf GS, et al. Egg-to-embryo transition is driven by differential responses to Ca^{2+} oscillation number. Dev Biol. 2002; 250(2): 280-291.
45. Ozil JP, Banrezes B, Tóth S, Pan H, Schultz RM. Ca^{2+} oscillatory pattern in fertilized mouse eggs affects gene expression and development to term. Dev Biol. 2006; 300(2): 534-544.
46. Rogers N, Halet G, Piao Y, Carroll J, Ko M, Swann K. The absence of a Ca^{2+} signal during mouse egg activation can affect parthenogenetic preimplantation development, gene expression patterns, and blastocyst quality. Reproduction. 2006; 132(1): 45-57.
47. Sousa M, Barros A, Tesarik J. Developmental changes in calcium dynamics, protein kinase C distribution and endoplasmic reticulum organization in human preimplantation embryos. Mol Hum Reprod. 1996; 2(12): 967-977.
48. Miller N, Biron-Shental T, Sukenik-Halevy R, Klement AH, Sharony R, Berkovitz A. Oocyte activation by calcium ionophore and congenital birth defects: a retrospective cohort study. Fertil Steril. 2016; 106(3): 590-596.e592.
49. Vanden Meerschaut F, D'Haeseleer E, Gysels H, Thienpont Y, Dewitte G, Heindryckx B, et al. Neonatal and neurodevelopmental outcome of children aged 3–10years born following assisted oocyte activation. Reprod Biomed Online. 2014; 28(1): 54-63.
50. Long R, Wang M, Yang QY, Hu SQ, Zhu LX, Jin L. Risk of birth defects in children conceived by artificial oocyte activation and intracytoplasmic sperm injection: a meta-analysis. Reprod Biol Endocrinol. 2020; 18(1): 123.
51. Bridges PJ, Jeoung M, Kim H, Kim JH, Lee DR, Ko C, et al. Methodology matters: IVF versus ICSI and embryonic gene expression. Reprod Biomed Online. 2011; 23(2): 234-244.
52. Ferrer-Buitrago M, Tilleman L, Thys V, Hachem A, Boel A, Van Nieuwerburgh F, et al. Comparative study of preimplantation development following distinct assisted oocyte activation protocols in a PLC-zeta knockout mouse model. Mol Hum Reprod. 2020; 26(11): 801-815.
53. Yin M, Yu W, Li W, Zhu Q, Long H, Kong P, et al. DNA methylation and gene expression changes in mouse pre-and post-implantation embryos generated by intracytoplasmic sperm injection with artificial oocyte activation. Reprod Biol Endocrinol. 2021; 19(1): 1-14.
54. Lu Q, Zhao Y, Gao X, Li Y, Ma S, Mullen S, et al. Combination of calcium ionophore A23187 with puromycin salvages human unfertilized oocytes after ICSI. Eur J Obstet Gynecol Reprod Biol. 2006; 126(1): 72-76.