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Original Research Article

Fertility outcome after intracytoplasmic sperm injection with surgically retrieved sperm in obstructive and non-obstructive azoospermia

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ABSTRACT

Background: Azoospermia is a highly upcoming subject in the last few decades. In the past, use of donor sperm was the only option providing a realistic chance of conception for couples affected by azoospermia. Introduction of sperm retrieval techniques and assisted reproductive technologies, especially intracytoplasmic sperm injection (ICSI), has provided these men a chance to father their genetically own child and changed the management approach significantly. The aim of this study was to compare the outcome of intracytoplasmic sperm injection (ICSI) of surgically retrieve sperms between couples with infertility due to male non-obstructive azoospermia (NOA) and obstructive azoospermia (OA).

Methods: It was a retrospective observational study and data analysis was conducted at Centre for Infertility and Assisted Reproduction (CIMAR), Edappal, Kerala, India from January 2018 to December 2021. The selection of cases was based on detailed history, physical examination, husband's semen analysis confirmed twice and hormone profile. During a period of four years, 754 azoospermic patients were diagnosed at our centre. In this study, female age <35 years considered as the inclusion criteria as female age plays a pivotal role for IVF/ICSI outcome, while patient in whom voluntary donor sperm used, patients in whom sperm retrieval failed, female age >35 years and female associated with any pathology which can alter the treatment outcome e.g., endometriosis, severe adenomyosis, diminished ovarian reserve, fibroid uterus were excluded from the study groups. On the basis of serum FSH, serum testosterone and testicular size and considering inclusion and exclusion criteria, patients were subdivided into two group as: group A (n=75) included patients with non-obstructive azoospermia and group B (n=75) included patients with obstructive azoospermia, underwent ICSI.

Results: Clinical pregnancy rate, fertilization and implantation rate were found to be higher in OA cases in comparison to those of NOA cases. Grade A embryo formation rate and miscarriage rate showed no significant difference.

Conclusions: As the cause of azoospermia is different in both the groups, the chances of achieving a successful outcome (fertilization rate, embryo formation rate, and clinical pregnancy rate) after ICSI are negatively affected by the type of azoospermia and are reduced in men with NOA in comparison to patients with OA.

Keywords: Azoospermia, FSH, OA, NOA, Testis

INTRODUCTION

Infertility has become a worldwide problem due to several reasons and according to Sharlip et al, it affects 15% of couples. In general, 50% of infertility cases are due to a solely female factor, while male factor accounts for 20-30%, and the remaining 20-30% is due to a combination of both male and female factors. There are various etiological factors for the male in infertility. Azoospermia is one of the cause male infertilities which comprise 1% of the cases.[1] Azoospermia is defined as the absence of spermatozoa in two different ejaculated semen samples after centrifugation (1000 gm for 15 minutes).[2] An accurate diagnosis of the cause of azoospermia is pivotal

and mandatory for these patients, as the treatment approach and clinical outcomes differs according to the etiology of azoospermia.

In clinical practice, azoospermia can be subdivided as obstructive or non-obstructive. Obstructive azoospermia is less common than NOA and occurs in 20-40% of men with azoospermia.[3] Testicular biopsy plays an important role in the diagnosis of type of azoospermia on the basis of histology, however hormone profiles and testicular size have been commonly used to predict the cause of azoospermia by using a cut off value of 7.6 mIU/ml for follicular stimulating hormone (FSH) and a testicular long axis of 4.6 cm.[4] Recently, concerns have been raised about the quality and genetic status of spermatozoa obtained from men with different etiologies of male infertility, the impact of these spermatozoa on the outcomes of assisted reproductive technology (ART). The aim of this study is to compare the outcome of intracytoplasmic sperm injection (ICSI) of surgically retrieve sperms between couples with infertility due to male non-obstructive azoospermia (NOA) and obstructive azoospermia (OA).

METHODS

It was a retrospective observational study and data analysis was conducted at Centre for Infertility and Assisted Reproduction (CIMAR), Edappal, Kerala, India from January 2018 to December 2021. The selection of cases was based on detailed history, physical examination, husband's semen analysis confirmed twice and hormone profile. During a period of four years, 754 azoospermic patients were diagnosed at our centre.

Inclusion and exclusion criteria

In this study, female age <35 years considered as the inclusion criteria as female age plays a pivotal role for IVF/ICSI outcome, while patient in whom voluntary donor sperm used, patients in whom sperm retrieval failed, female age >35 years and female associated with any pathology which can alter the treatment outcome e.g., endometriosis, severe adenomyosis, diminished ovarian reserve, fibroid uterus were excluded from the study groups.

On the basis of Serum FSH, serum testosterone and testicular size and considering inclusion and exclusion criteria, patients were subdivided into two group as: group A (n=75) included patients with non-obstructive azoospermia and group B (n=75) included patients with obstructive azoospermia, underwent ICSI.

Controlled ovarian stimulation was done using long GnRH agonist protocol. HCG was given for final maturation of oocyte and oocyte retrieval was done 36 hours later. The quality of oocyte was assessed morphologically and ICSI was done. In obstructive azoospermic patients, PESA was done on the day of oocyte collection. If PESA failed to extract any spermatozoa, testicular sample was taken by TESA and used for ICSI. In male's non obstructive azoospermia, micro-TESE was planned one day prior to OPU. Pregnancy was determined by serum beta hCG levels on day 14 after embryo transfer. Clinical pregnancy was confirmed by ultrasonography at 6 weeks.

Statistical analysis

Data was analysed using SPSS version 20. All categorical variables were summarized as frequency with percentages. All continuous variables were summarized using mean (SD) or median (IQR) based the normality of the data. The comparison of continuous outcomes with two groups was done using an independent t test. The comparison of categorical outcomes between the groups was analysed using chi-squared test. A p value less than 0.05 were considered statistically significant.

RESULTS

A total of 150 patients were studied. Out of these, 75 were included in non-obstructive azoospermic group and 75 were in OA group. Baseline characteristics were compared in both the groups (Table 1). The mean age of the patients in group A and B was 35.63±5.75 and 34.57±4.77 (p value- 0.224) respectively, with no statistically significant difference. The mean volume of testis in both the groups was analysed. In the NOA group, the mean testicular volume of each testis was 7.8±0.98 whereas in the OA group, the mean testicular volumes were 11.8±1.23, respectively. Hence, there was significant difference in bilateral testicular volumes between both the groups (p<0.001). In the NOA group, the mean serum testosterone and serum FSH were 316.54±110.3 and 12.10±8.87, respectively. In the OA group, the mean serum testosterone and serum FSH were 495.85±99.36 and 3.43±1.60 respectively. This difference in serum testosterone and serum FSH levels among both the groups was found statistically significant (p<0.001). The sperm retrieval method used in NOA patients were TESA in 46.6% (35/75) and micro-TESA in 53.3% (40/75) while in OA patients' sperm were retrieved through PESA in 81.3% (61/75) and TESA in 18.6% (14/75).

Table 1: Male characteristics feature of the group A and group B of the study.

Male characteristics	Group A (NOA)	Group B (OA)	p value
Age	35.63±5.75	34.57±4.77	0.224
Avg. testicular volume	7.8±0.98	11.8±1.23	<0.001
Serum FSH	12.10±8.87	3.43±1.60	<0.001
Serum testosterone	316.54±110.3	495.85±99.36	<0.001

Female age, antral follicular count and duration of infertility were not different in the groups of NOA, and OA. There were no significant differences in the number and maturity of Oocytes retrieved in each of the groups.

The normal two-pronuclear zygote (2PN) and high-quality embryos rates were lower in the NOA (4.5±2.8 and 4.56±0.75, respectively) and OA (5.6±2.4 and 5.96±0.93, respectively p<0.001) groups. The mean number of transferred embryos was similar among the groups. The fertilization rate, clinical pregnancy rate and implantation rate after ICSI were 55%, 33.3% and 14% in NOA group and 72%, 61.3% and 29% in OA respectively, which were statistically significant (p value <0.001) (Table 3). The miscarriage rate in each group A and B were 16% (n=4) and 21.7% (n=10) respectively (p value 0.562).

Table 2: Female characteristics feature and outcomes of the stimulation cycle in the both group A and B of the study.

Female characteristics	Group A (NOA)	Group B (OA)	P value
Age	27.21±4.61	26.80±4.81	0.175
AFC	17.7±9.5	21.7±11.8	0.09
Stimulation cycle and ICSI outcomes			
Duration of infertility	4.3±3.2	5.1±3.7	0.53
Stimulation duration (days)	11.2±1.9	10.7±2.2	0.23
Serum estrogen on the day of trigger	2745±455	2780±380	0.28
Serum progesterone on the day of trigger	2.1±1.0	1.9±0.9	0.76
No. of oocytes collected	11.8±6.1	9.9±5.8	0.19
No. of M II ooyctes	8.7±4.3	7.4±3.3	0.14
No. of pronuclear zygote (2PN)	4.5±2.8	5.6±2.4	<0.001
No. of high grade embryos	4.56±0.75	5.96±0.93	<0.001

Table 3: Clinical outcomes of ICSI in group A and group B.

ICSI outcomes	Group A (NOA) (%)	Group B (OA) (%)	P value
Fertilization rate	55	72	<0.001
Clinical pregnancy rate	33.3	61.3	<0.001
Implantation rate	14	29	<0.001
Miscarriage rate	16	21.7	0.562

DISCUSSION

Azoospermia is diagnosed when at least two semen samples obtained more than two weeks apart are examined, analysed and failed to contain any sperm according to 2010 World Health Organization guidelines.[5]

The approach to azoospermic patients has changed significantly with the introduction of sperm retrieval techniques and assisted reproduction especially ICSI. ICSI has made it possible to achieve good pregnancy results in these patients and gave an opportunity to own their genetic child. In contrast to the patients with OA where surgical correction is possible in selected cases, majority of patients with NOA surgical retrieval of the sperm is the only option to achieve a pregnancy. Obstructive azoospermia is the result of a blockage of the male reproductive tract, leading to a complete absence of sperm in the ejaculate, and accounts for approximately 40% of all cases of azoospermia.[6]

Obstruction may be congenital or acquired and may include one or more segments of the male reproductive tract: epididymis, vas deferens, and ejaculatory ducts. Congenital causes of obstructive azoospermia include congenital bilateral absence of the vas deferens (CBAVD) and idiopathic epididymal obstruction. Acquired causes of obstructive azoospermia include vasectomy, infection, trauma, or iatrogenic injury. Non-obstructive azoospermia (NOA) is characterized by a complete absence of spermatozoa in semen because of minimal or no spermatogenesis. Possible causes are genetic disorders such as sexual chromosomal abnormalities, translocation and micro deletions of the Y chromosome, cryptorchidism, testicular torsion, radiation and toxins.[7] The aim of this study was not to compare these various methods of surgically retrieved sperm and their etiologies but to compare the fertility outcome after ICSI in surgically retrieved sperm between OA and NOA.

On comparison to ICSI outcomes, no significant difference was found in total number of collected oocytes and number of matured oocytes among both the groups (p value- 0.19 and 0.13 respectively). In our study, we noted a lower rate of fertilization (FR) in the NOA group in comparison to the OA group (p<0.001). Similarly, a lower cleavage stage embryo formation was also observed in NOA group (p value <0.001). Ghanem et al in a meta-analysis of five studies reported a significantly higher FRs and significantly higher proportion of grade A embryos in patients with OA and similar results were also shown by various studies.[8-10]

On comparing the implantation rate in the present study, significant difference was present statistically between NOA and OA with 14% and 29% respectively (p value <0.001). A study conducted by Vernaeve et al, compared the cycles of males having NOA and cycles with OA and found the implantation rate was higher in males with OA (8.6% versus 12.5%) and similar results were shown in a study of Tehraninejad et al.[11,12] This indicates that implantation potential of embryos derived from ICSI with surgically retrieved sperms in patients with OA was better than patients with NOA.

Finally comparing the clinical pregnancy rate (CPR) and miscarriage rate (MR) between the two groups, our results

showed significant difference in the CPR (p value <0.001) however, MR is insignificant statistically (p value 0.562). A study conducted by Talreja et al showed higher clinical pregnancy rate in OA group (68.8%) than NOA group (42.9%) which were akin to our results.[13] A similar finding was reported by He et al in ICSI cycles with OA and with NOA, p value =0.43328.[14] According to the results, it reflects that embryo formation rate, implanatation rate and clinical pregnancy rates were lower in NOA patients which can be can be explained by the fact that testicular spermatozoa from have a higher tendency to carry defects related to the centrioles and genetic material, which impairs the capability of the male gamete to trigger the formation and development of a zygote and good quality embryo by dysregulation and dysfunction of oocyte activating factors, centrosomes, and cytoskeletal components.[15,16]

Tehraninejad et al found a miscarriage rate of 9.7% in OA and 8% in NOA, p value =0.77624 and some similar results were also showed which were comparable to our study.[12,17,18] In contrast to our study, Pasqualotto et al found miscarriage rate was higher in NOA compared to OA (p value <0.05).[19] It has been shown that miscarriage rates may be higher in men with NOA due to aneuploidy and DNA damage in NOA spermatozoa that may contribute to a late paternal effect, leading to pregnancy loss.[20] The limitation of our study is that it was a retrospective study.

CONCLUSION

As the cause of azoospermia is different in both the groups, the chances of achieving a successful outcome (fertilization rate, embryo formation rate, and clinical pregnancy rate) after ICSI are negatively affected by the type of azoospermia and are reduced in men with NOA in comparison to patients with OA.

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