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Original Article

Clinical outcomes and development of children born to couples with obstructive and nonobstructive azoospermia undergoing testicular sperm extraction-intracytoplasmic sperm injection: A comparative study

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ABSTRACT

Objective: To evaluate and compare the clinical outcomes and development of children born between obstructive azoospermia (OA) couples and nonobstructive azoospermia couples (NOA) after testicular sperm extraction (TESE) and intracytoplasmic sperm injection (ICSI).
Materials and methods: Data were collected from infertile couples suffering from azoospermia who underwent TESE and ICSI from January 2001 to December 2009 at Chang Gung Memorial Hospital, Taiwan. A total of 154 ICSI cycles were performed using extracted testicular sperm from men with obstructive azoospermia (67 ICSI cycles) and men with nonobstructive azoospermia (87 ICSI cycles). Retrospective analysis of clinical outcomes and development of children born after TESE-ICSE between obstructive azoospermia couples and nonobstructive azoospermia couples.
Results: The assisted reproductive technology (ART) result between OA and NOA groups, including age, E2 level on hCG day, number of oocytes retrieved, normal fertilization rate, zygote Grade 1 score distribution, number of top-quality embryos transferred, clinical pregnancy rate per transfer, chemical pregnancy rate per transfer, implantation rate, live birth rate per transfer, and abortion rate per transfer, were all similar. Thirty-one live births resulted from 67 ICSE cycles in the OA group and 33 live births from 87 ICSE cycles in the NOA group. The obstetric and perinatal outcomes were similar between the groups, and children conceived by using ICSI were generally healthy without raised tendency of major birth defect and development impairment.
Conclusion: In our study, there were no differences in the fertility rate and clinic pregnancy rate between the OA and NOA groups using TESE-ICSI. Also, the clinical outcomes and development of children were similar between the OA and the NOA groups using TESE-ICSI.

Introduction

Azoospermia is uncommon but not rare, occurring in about 2% of men in the general population and 10–20% of men treated at infertility centers [1,2]. Azoospermia has different etiologies, previously described as pretesticular, testicular, and posttesticular; although physiologically correct, this classification is not always practical for making decisions regarding treatment. Rather, the classification of azoospermia as obstructive (nondefective spermatogenesis) and nonobstructive (defective spermatogenesis) is better for determining specific treatment options available to individual patients [3]. At present, even men without any sperm in the ejaculate due to obstructions or problems in sperm production, can father a biological child. Testicular sperm extraction (TESE) remains the oldest and most informative diagnostic modality to

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differentiate between men with obstructive and nonobstructive azoospermia [4–8].

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), and the health and well-being of offspring born to these men [9,10]. Intracytoplasmic sperm injection (ICSI) has been shown to be effective in the treatment of male infertility, suggesting that this technique may overcome the problems associated with the poor quality and the low quantity of spermatozoa [8,11]. The comparative success rates of ICSI in OA and NOA men is unclear, with several studies reporting similar fertilization and pregnancy rates, whereas others found that ICSI outcome rates were lower in NOA than in OA patients [12–14].

Since chromosome abnormalities may be associated with male infertility, genetic factors have been assessed in OA and NOA men. Prenatal examinations found higher rates of abnormal karyotypes in children conceived from NOA than from OA sperm [9,14]. The rate of aneuploidic sperm passed to offspring was higher in men with NOA than in those with OA [15–17], and an increase in meiotic errors was found to be associated with poor testicular endocrine factor [18]. Moreover, the rate of anomalies in sex chromosomes was higher in the sperm of men with NOA than with OA [19–21]. Less is known, however, about the efficacy of TESE-ICSE performed with spermatozoa from men with OA and NOA, or about clinical outcomes and the development of children born to these couples. We therefore evaluated and compared the clinical outcomes and development of children born to couples with OA and NOA undergoing TESE-ICSI.

Materials and methods

Patient population

Data were collected from azoospermic couples who underwent ICSI and transcervical embryo transfer (ET) from January 2001 to December 2009 at Chang Gung Memorial Hospital, Taiwan. Prior to surgical extraction of testicular spermatozoa, an experienced urologist performed a complete physical examination of the genitalia of all men with OA and NOA, including formal scrotal exploration. Testicular spermatozoa were extracted by TESE from these men with OA and NOA, frozen, thawed, and utilized in 67 and 87 ICSI cycles, respectively. These techniques have been described in detail [8,22]. Endocrinology evaluation included assaying the concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. All testicular biopsy samples were examined in our pathology department. A diagnosis of OA required confirmation of normal spermatogenesis by testicular biopsy. NOA was pathologically categorized as due to spermatogenic hypoplasia, maturation arrest, cryptorchidism, or testicular atrophy. We excluded cases with abnormal karyotyping, e.g., Klinefelter syndrome (47, XXY). We also excluded cases of testis atrophy and biopsies where no spermatozoa were obtained. Analysis of chromosome aberrations were not performed routinely on our male patients undergoing TESE.

All women included in this study had undergone a routine infertility work-up. Informed consent for the ICSI-TESE procedures were obtained from all study participants. The study protocol was approved by the Ethics Committee and the Institutional Review Board of Chang Gung Memorial Hospital.

Sperm retrieval, preparation, cryopreservation, and ICSI technique

The cryo-TESE procedure, including extraction of testicular tissue, preparation of testicular sperm, and cryopreservation of testicular spermatozoa, was performed as described [23,24]. Almost 90% of the post-thawed spermatozoa showed at least occasional tail twitching with normal morphology. The ICSI procedure was performed as described, except that the sperm drop preparation did not contain polyvinylpyrrolidone (PVP) [22,25–27].

Assessment of fertilization, embryo culture, and zygote and embryo grading

Our standardized clinical methodology, including ovarian hyperstimulation following a standard downregulation regimen and the performance of all procedures by a single team of embryologists, has been described previously [28,29]. Fertilization was defined as a zygote with two pronuclei (2PN). The oocytes were cultured for 16–18 hours, after which they were assessed for the presence of pronuclei and then scored according to the Z-score scoring system [8,28].

Embryos were sequentially cultured in G1-2TM and G2-2TM media (Scandinavian IVF Science). Blastomere number and regularity were analyzed on Day 3. After culture for 2 days in G2-2TM media, blastocyst formation was evaluated and scored based on the state of blastocyst expansion, the consistency of the inner cell mass, and the presence of trophectoderm cells.

"Top-quality" embryos were those that showed (1) Grade 1 embryo morphology on Day 3 (8 cells, blastomeres of equal size, and no cytoplasmic fragments), and (2) blastocysts on Day 5 (full blastocysts; inner cell mass with numerous tightly packed cells; and trophectoderm with many cells forming a cohesive epithelium).

Establishment and follow-up of pregnancy

Beginning on the day of oocyte retrieval, luteal-phase supplementation with micronized progesterone (Utrogestan, 800 mg/day intravaginally; Piette International Laboratories) was started. Blastocysts, consisting of more than three 8-cell embryos, were transferred on Day 5 and human chorionic gonadotropin (hCG; 500 IU/day) was routinely administered to all couples 6 days after oocyte recovery. Chemical pregnancy was defined as the presence of hCG in urine 2 weeks after transfer, and clinical pregnancy was defined by the presence, on routine transvaginal ultrasonography performed at 7 weeks of gestation on a gestational sac; if present, patients were given micronized progesterone supplementation for an additional 4 weeks.

Maternal, infant, and children outcome survey

The medical records of all live births from TESE-ICSI were reviewed to assess maternal and infant outcomes and the development of the latter. Obstetric events included preeclampsia, eclampsia, gestational diabetes, preterm labor, and cesarean delivery. Adverse infant outcomes included low Apgar score, fetal death, preterm delivery, major birth defects, fetal growth restriction, intracranial hemorrhage, sepsis, and the need for mechanical ventilation and intensive ICU care. Birth defects were grouped into four categories—congenital heart defects and gastrointestinal, musculoskeletal, and chromosomal anomalies—with only those of major morphologic importance or showing functional impairments considered anomalies. Preterm birth was defined as birth at a gestational age <32 weeks, and fetal growth restriction (small-for-gestational age) was defined as a birth weight under the third percentile in the corresponding standard population stratum. Intrauterine death at gestational age >20 weeks or at birth weight >500 g was defined as fetal death. One and 7 minute Apgar scores <5 and <7, respectively, were defined as low.