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CASE REPORT

Intracytoplasmic sperm injection in male renal transplant recipients☆

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KEYWORDS

Renal transplant;
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Abstract *Objective:* In this study, we reviewed the reproductive outcomes following ICSI in 5 couples where the male partners had undergone renal transplantations. Chronic renal failure and dialysis may adversely affect male reproductive function resulting in severely depressed semen parameters or even azoospermia, which maybe further adversely affected by the immunosuppression taken from after transplantation.

Study design: Case report.

Setting: A private fertility clinic.

Patients: The study included five infertile couples where the male partners were the recipients of renal transplants, 3–15 years prior to having ICSI treatment. All couples suffered from male factor infertility, with diagnoses of; azoospermia, asthenoteratozoospermia, oligoasthenoteratozoopsermia.

Results: In the 5 case reports 5 ICSI and 3 FET treatment procedures were completed. In all but one of the cases grade 1 quality embryos were obtained and transferred. From the 8 embryo transfers performed 4 pregnancies were obtained, one miscarried at 8 weeks and 3 resulted in live births.

Abbreviations: COS, controlled ovarian stimulation; OPU, oocyte pickup; ICSI, intracytoplasmic sperm injection; FET, frozen embryo transfer; OHSS, ovarian hyperstimulation syndrome; GnRH, gonadotropin releasing hormone; rFSH, recombinant follicle stimulating hormone; hMG, human menopausal gonadotropin; hCG, human chorionic gonadotropin; E2, estrogen; P4, progesterone; β-hCG, beta-human chorionic gonadotropin

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Conclusions: In this study, we showed that pregnancy and normal live birth were possible following ICSI treatment for male factor infertility, where male partners had had renal transplants and were under immunosuppressive therapy.

1. Introduction

In the past, the primary objective of therapy for patients at end-stage renal disease was largely restricted to prolonging life. However, today the objective is not only to prolong life, but also to increase the quality of life in these patients, which includes the restoration of reproductive and sexual functions.

At end-stage renal disease that requires dialysis treatment, there is normally an associated reduction in reproductive function. The cause of the infertility is not entirely clear, but is probably multifactorial. Extra-hypothalamic, hypothalamic and hypophyseal axis abnormalities are encountered in systemic diseases, such as renal failure, that may lead to the deterioration of testicular function through impaired steroidogenesis and spermatogenesis. Sperm parameters may remain depressed during dialysis, but following successful renal transplantation some improvement in the parameters may occur (1,2). Sperm motility is one parameter that has been seen not to measurably improve after renal transplantation. In addition, immunosuppressive drugs required following renal transplantation may too, adversely affect sperm parameters.

In most of cases following renal transplantation and immunosuppressive therapy, the only hope of successful conception for these men would be with the use of ICSI. To date, there have only been two published case reports describing the management of fertility in couples affected by these complications (3,4). In the one case report, the experience of obtaining a successful twin pregnancy in a dual-transplant couple with the use of ICSI was described (3). In the other, the reproductive outcomes following ICSI treatments in 3 couples where the male partners had renal transplants was described. In 2 of the 3 couples a pregnancy was obtained (4).

We present here the outcomes following ICSI in five couples with male infertility, in which the male partners were kidney transplant recipients.

2. Materials and methods

All male partners underwent multiple standard semen analyses, where sperm morphology, sperm count and sperm motility were assessed and diagnosed according to the World Health Organization criteria (5). Sperm morphology was evaluated according to the strict criteria proposed by Kruger/Tygerberg and adopted by the World Health Organization (5), using Papanicolaou stain. In the cases of azoospermia, the semen ejaculates were centrifuged and the pellets examined for the presence of sperm.

Surgical sperm retrieval was performed according to the conventional testicular sperm extraction (TESE) procedure, with micro-TESE performed if required. The choice of whether one or both testes were biopsied and the number and size of the biopsies taken was dependent on testicular size and consistency and the presence and number of sperms. Testicular tissue and or seminiferous tubules were processed and the supernatants examined for sperm.

All assisted conception cycles were performed with ICSI inseminations. COS was performed using a GnRH agonist (Leuprolide acetate; Lucrin daily, Abbott, Turkey) protocol with a combination of rFSH (Gonal-F, Merck Serono; Pereon, Merck Sharp Dohme) and hMG (Menopur, Ferring pharmaceuticals). Patient's response to COS was monitored by serial transvaginal ultrasound follicular measurements. Ovulation was induced by hCG (Ovidrel, Merck Serono, 250 μg/0.05 ml) trigger when at least three follicles reached 17 mm in diameter. Transvaginal ultrasound-guided oocyte retrieval was performed 36 h after ovulation induction. The oocytes retrieved were denuded and all mature oocytes were fertilized by ICSI. All embryo replacements were performed under ultrasound guidance on day 2 of embryo development. Embryos were graded on a scale of 1–4 (1 being best) based on; cell number, blastomere size and equivalence, and percentage of fragmentation (6). The luteal phases of all cycles were supplemented with E2 (Estrofem, Novo Nordisk, 2 mg BD) and P4 (Crinone, Merck Serono, 8% BD) and continued for at least 9 weeks of gestation if pregnant.

Embryos were cryopreserved using a standard slow cooling method (Freeze- and thaw-kits, Vitrolife) where embryos were washed through dehydrating solutions before being loaded into cryo-vessels. The cryo-vessels were then placed in the chamber of a programmable freezing machine which slowly reduces the temperature to a set threshold temperature. During the initial cooling phase ice nucleation (seeding) was induced. At a set time and temperature the cryo vessels were plunged into liquid nitrogen and cryo-stored. On the day of the thawing the cryo-vessels were removed from the cryo-tanks and the embryos allowed to rapidly thaw and washed through solutions promoting rehydration.

All frozen embryo transfer (FET) cycles were performed after endometrial preparation and synchronization using time supplementation with estrogen (E2, Estrofem, Novo Nordisk, 2 mg BD) and progesterone (P4, Crinite, Merck Serono, 8% BD). Preparation of the endometrium was started within 4 days of the patient's day 1 of menstrual cycle and achieved in a step-up regime (2–8 mg). Endometrial readiness was determined on the 14th day by measuring endometrial thickness (>6 mm). If ready, daily progesterone supplementation was started on the 15th day and the FET procedure scheduled for 2 days later. The embryo transfer was performed as in the fresh embryo transfer.

A clinical pregnancy was defined as an ultrasound confirmed fetal sac 7 weeks after embryo transfer. All the male partners participating in the treatment continued to use immunosuppressive medications over the treatment period.

3. Results

The male diagnosis, the couple's period of infertility, the number of years since the male partner had the renal transplant procedure and the immunosuppressives been taken by each male partner are listed in Table 1.

3.1. Case 1

A 22-year-old woman presented with a 2 year history of infertility with a 32-year-old azoospermic male partner, who had undergone a successful renal transplantation procedure 4 years previously, because of chronic renal disease. Sperm were successfully collected from testicular tissue obtained from a TESE procedure. Twenty oocytes were collected following COS. Fifteen normally fertilized oocytes were obtained from insemination by ICSI. Fifteen embryos of differing grades developed from the zygotes, 9 were of grade 1 quality. Three grade-1 embryos were transferred on day 2 and the remaining 6 grade-1 embryos were cryopreserved. Twelve days after embryo transfer a negative β-hCG result was obtained. Two months later 3 grade-1 embryos were transferred on day 2 of a FET treatment cycle. From the FET a positive β-hCG (470 IU/ml) result was obtained. A transabdominal ultrasound scan done at 7 weeks of gestation revealed two gestational sacs in the uterus, both with normal fetal cardiac activity. Healthy twins were delivered to the couple at 37 weeks of gestation.

3.2. Case 2

A 25-year-old woman presented with a 3 year history of infertility with a 32-year-old male partner suffering from mild asthenoteratozoospermia (63 million sperm/ml, 28% progressive motility, 2% normal sperm morphology). The male partner had undergone a renal transplantation procedure 15 years previously. However, was still suffering from chronic renal failure requiring daily ambulatory peritoneal dialysis. Twenty-three oocytes were collected from COS. Nineteen normally fertilized oocytes were obtained from insemination by ICSI. Nineteen zygotes divided as embryos, 15 developing as grade 1 embryos. Following COS the female partner developed ovarian hyperstimulation syndrome (OHSS) and all embryos of suitable quality were cryopreserved on day 2. Two months later 3 grade 1 embryos were transferred on day 2 of a FET treatment cycle. From the FET a positive β-hCG (153 IU/ml) was obtained. A transabdominal ultrasound scan done at 7 weeks of gestation revealed two gestational sacs in the uterus, but only one had normal fetal cardiac activity. A healthy baby was delivered to the couple at 30 weeks of gestation. Two years subsequent to her 1st FET she had another FET treatment cycle in which 2 grade 1 embryos were transferred on day 2. A second pregnancy was followed by a positive day 14 β-hCG (582 IU/ml) and a 7 week transabdominal ultrasound scan revealing 2 gestational sacs in the uterus, both with fetal cardiac activity. Healthy twins were delivered to the couple at 36 weeks of gestation.

3.3. Case 3

A 35-year-old woman presented with a 6 year history of infertility with a 37-year-old male partner suffering from severe oligoasthenoteratozoospermia (1.9 million sperm/ml, 26% progressive motility, 0% normal sperm morphology). The male partner had undergone a renal transplantation procedure 3 years previously, because of chronic renal disease. Fifteen oocytes were collected following COS. Eleven normally fertilized oocytes were obtained from insemination by ICSI. Eleven relatively poor quality embryos developed from the zygotes, 2 embryos were of grade 2 quality and the rest were of grade 4 quality. The 2 grade embryos were transferred on day 2. Twelve days after the embryo transfer a negative β-hCG result was obtained.

3.4. Case 4

A 34-year-old woman presented with a 2 year history of infertility with a 40-year-old azoospermic male partner, who had undergone a successful renal transplantation 4 years previously, because of chronic renal disease. Sperm were successfully collected from testicular tissue obtained from a TESE procedure. Four oocytes were collected following COS. Three normally fertilized oocytes were obtained from insemination by ICSI. Three zygotes developed to embryos on day 2, 2 of them were of grade 1 quality. The 2 grade 1 embryos were transferred on day 2. Twelve days after the transfer a positive β-hCG (275 IU/ml) was obtained with the 7 week abdominal ultrasound scan revealing 2 gestational sacs in the uterus, both with fetal cardiac activity. The pregnancy was unfortunately miscarried at 8 weeks. One year after their 1st ICSI cycle the coupled embarked on another. Two oocytes were collected following COS, 2 were normally fertilized and 2 grade 1 quality embryos developed on day 2. The 2 grade 1 embryos were transferred on day 2. Twelve days after the transfer a negative β-hCG result was obtained.

Table 1 Renal transplant patient demographics.

	Spermiogram	Infertility years[a] (yrs)	Transplant years[b] (yrs)	Immunosuppressive 1	Immunosuppressive 2	Immunosuppressive 3
Case 1	Azoospermia	2	4	Cyclosporine 125 mg/d	Prednisolone 5 mg/d	Mycophenolate 1440 mg/d
Case 2	Asthenoteratozoospermia	3	15	Tacrolimus 4 mg/d	Prednisolone 5 mg/d	Mycophenolate 720 mg/d
Case 3	Oligoasthenoteratozoospermia	6	3	Cyclosporine 200 mg/d	Prednisolone 5 mg/d	Mycophenolate 720 mg/d
Case 4	Azoospermia	2	4	Tacrolimus 4 mg/d	Prednisolone 5 mg/d	–
Case 5	Oligoasthenoteratozoospermia	2	5	Tacrolimus 2 mg/d	Prednisolone 5 mg/d	Mycophenolate 1440 mg/d

[a] Infertility duration.
[b] The number of years since the kidney transplantation procedure.

3.5. Case 5

A 30-year-old woman presented with a 2 year history of infertility with a 43-year-old male partner suffering from severe oligoasthenoteratozoospermia (4.1 million sperm/ml, 28% progressive motility, 0% normal sperm morphology). The male partner had undergone a renal transplant procedure 5 years previously, because of chronic renal disease. Fifteen oocytes were collected following COS. Eight normally fertilized oocytes were obtained from an ICSI insemination. Eight embryos developed from the zygotes, one grade 1 quality embryo and all the rest grade 2 quality embryos. Two embryos were transferred on day 2. Twelve days after the transfer a negative β-hCG result was obtained.

4. Discussion

Chronic renal disease and failure may adversely affect male reproductive function. Changes to the function of the hypothalamic–pituitary–ovarian/testis axis in patients with chronic renal failure or severe hepatic dysfunction may result in anovulation or azoospermia. Uremia causes a significant decline in reproductive function and sperm quality which may lead to infertility or even sterility in humans (7). The earlier the onset, pre or post-pubertal, and the longer the duration of uremia, the more impairment the reproductive function in the human (8).

Although transplantation may reverse many disease impaired functions, there is not a lot of substantiated evidence in the published literature on whether male reproductive function may be restored. Statistically significant differences were found when duration of dialysis, FSH levels, sperm counts, morphology, and motility between post-transplant fertile and infertile patients were compared (9). Long lasting or permanent damage to testicular function may mean that men following renal transplantation may require IVF treatment more often than not. Normozoospermia was seen in 47.3% of the patients, asthenozoospermia in 18.2% oligozoospermia in 14.5%, while oligoteratozoospermia, asthenoteratozoospermia, oligoasthenozoospermia, oligoasthenoteratozoospermia, and azoospermia were seen in the rest (9).

In addition, immunosuppression after transplantation may also have an effect on male reproductive function. The effect may be dependent on the type or types, the dosages taken and the duration before treatment. Cyclosporine, tacrolimus, and sirolimus are commonly used in renal transplant recipients to prevent rejection. Spermatogenesis was also severely impaired as indicated by low total sperm counts along with reduction of sperm motility and increase in sperm abnormality after treatment with these agents, which may lead to male infertility.

A rat model of unilateral nephrectomy, demonstrated that long-term oral administration of both cyclosporine and sirolimus at doses equivalent to the therapeutic levels used for post-renal transplant patients significantly affects testicular development and the hypothalamic–pituitary–gonadal axis (10). On the other hand, treatment with therapeutic dose of tacrolimus only induced mild reduction of sperm count without histological evidence of testicular injury. It was also shown that duration of exposure to corticosteroids or cyclosporine combined with azathioprine contributes to sperm dysfunction in peripubertal transplanted boys (8).

We presented five male renal transplant recipients' infertility who underwent intracytoplasmic sperm injection (ICSI) and embryo transfer (ET). Two of the 5 men who had renal transplants were azoospermic. Three successful pregnancies, resulting in live births were achieved from the 8 ART treatments performed.

Conflict of interest

None declared.

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