CASE REPORT

Successful twin pregnancy in a dual-transplant couple resulting from in-vitro fertilization and intracytoplasmic sperm injection

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To our knowledge, there has been only one reported case in this group. There are numerous reports of successful pregnancy following liver transplantation. Little information is available regarding the incidence and management of infertility in transplant recipients, particularly the use of artificial reproductive technologies. We present a case of a successful twin pregnancy resulting from in-vitro fertilization with intracytoplasmic sperm injection (IVF/ICSI) in a liver transplant recipient, whose partner was a renal transplant recipient with severe oligozoospermia. With careful evaluation and monitoring, and the involvement of appropriate consultants, artificial reproductive technologies can be safely used in transplant recipient couples experiencing infertility.

Key words: infertility/intracytoplasmic sperm injection/in-vitro fertilization/organ transplantation/pregnancy

Introduction

There have been numerous reports in the literature of successful pregnancy occurring following liver transplantation (Radomski et al., 1995; Pruvot et al., 1997; Casele and Laifer, 1998). With advancements in transplantation medicine, and particularly in immunosuppressant medication, it is no longer necessary to discourage pregnancy in most female liver transplant recipients of reproductive age. While menstrual disorders such as oligomenorrhea, amenorrhea, irregular bleeding, and menorrhagia are common in women prior to transplant, normal menstrual function resumes in the majority following successful transplantation (Cundy et al., 1990; de Koning and Haagsma, 1990; Laifer and Guido, 1995; Mass et al., 1996). Almost no information is available regarding the incidence and management of infertility problems in this population. With more and more transplant recipients attempting to conceive, couples with infertility due to factors other than anovulation (i.e. tubal blockage, male factor) will invariably present. This raises the issue of the use of artificial reproductive technologies in this group.

To our knowledge, there has been only one reported case of the use of artificial reproductive technologies in a transplant patient: a renal transplant recipient who underwent in-vitro fertilization (IVF) because of tubal blockage. This patient successfully conceived and delivered twins (Lockwood et al., 1995). We present a case of a successful twin pregnancy resulting from IVF with intracytoplasmic sperm injection (IVF/ICSI), in a liver transplant recipient whose partner was a renal transplant recipient with severe oligozoospermia. While a successful twin pregnancy in a liver transplant patient has been reported (Grow et al., 1991), we believe this is the first reported case of the use of artificial reproductive technologies in a liver transplant patient, and a dual-transplant couple.

Case history

A 22 year old, nulliparous woman presented with her partner to our clinic with a desire to become pregnant. At age 18 years, she underwent a liver transplant for Budd-Chiari syndrome. Medications since the transplant included cyclosporine and coumadin. Since the transplant, she had been followed by gynaecology for recurrent, severe menorrhagia, at times necessitating hospital admission and blood transfusions. Medical therapy, including oral contraceptives, had been unsuccessful, and she was subsequently started on a gonadotrophin-releasing hormone (GnRH) agonist; Lupron (Abbott, Donal, Canada), with oestrogen-progestin addback, to suppress menstruation. Endometrial ablation was planned when she had completed her family.

This couple’s wish for fertility was complicated by a severe male-factor problem: retrograde ejaculation and profound oligozoospermia. Her partner, age 26 years, had hereditary polycystic kidney disease, and had undergone several urinary tract operations since childhood, and finally a renal transplant. Unfortunately, acute rejection of the transplanted kidney occurred, and he was now on dialysis. Two years previously, an analysis of semen recovered from the bladder revealed a total motile sperm count of 0.005×10⁶ after swim-up. Now that he was on dialysis, and anuric, adequate sperm recovery from the bladder was not possible. Consultation with andrology experts confirmed that spermatozoa would now have to be recovered through epididymal aspiration, and ICSI performed on oocytes recovered from his partner after ovulation induction.

Prior to initiating an IVF/ICSI cycle, consultations were obtained from perinatology, haematology and genetics, in
particular to address management of the patient’s anticoagulation, implication of her transplant status on pregnancy (and vice versa), and genetic implication of her partner’s polycystic kidney disease.

One month prior to starting her cycle, her partner underwent epididymal aspiration. A volume of 0.5 ml with three spermatozoa/high power field was obtained, and then frozen.

Two weeks before the start of her cycle, her coumadin was discontinued, and she was started on low molecular weight heparin (175 IU/kg). Oestradiol; estrace (Roberts Pharmaceuticals, Mississauga) 2 mg was started for endometrial priming, since she was already on a GnRH agonist; Lupron (Abbott). Gonadotrophins; Fertinorm (Serono, New Bedminster), 150 IU/day were started 2 weeks later, and she was monitored every 2 days with transvaginal ultrasound and blood measurements [oestradiol and luteinizing hormone (LH)]. On day 15, with seven mature follicles (18 mm) and oestradiol of 3712 pmol/l, human chorionic gonadotrophin (HCG) 10 000 IU was administered. Forty-eight hours prior to transvaginal oocyte retrieval, low molecular weight heparin was discontinued, and was restarted 24 h following the retrieval. Retrieval was carried out uneventfully under i.m. sedation with morphine and dimenhydrinate, and bleeding was not excessive. Seven oocytes were recovered, and five achieved fertilization with ICSI using the previously cryopreserved epididymal spermatozoa. Three embryos progressed to an 8-cell stage, while the remaining two arrested in development. Seventy-two hours following retrieval, embryo transfer of three good quality embryos (two 8-cell, grade 2 embryos, one 8-cell, grade 3 embryo) occurred, and progesterone vaginal suppositories were started (50 mg q.i.d). Two weeks following embryo transfer, the patient had a serum HCG of 682 IU/l. An intrauterine twin pregnancy was confirmed by transvaginal ultrasound 6 weeks post-transfer.

The patient was closely monitored throughout her pregnancy, and received routine antenatal care with respect to sonographic screening. Low molecular weight heparin was continued throughout the pregnancy, which was uneventful until 28 weeks when she developed mild pre-eclampsia and discordant growth of the twins requiring hospitalization. Preterm premature rupture of membranes, and subsequent preterm labour occurred at 34 weeks. Caesarean section was performed for a footling breech presentation. Twin boys weighing 1460 g and 2120 g with good APGAR scores, were delivered. Unfortunately, the patient experienced a delayed postpartum haemorrhage from her uterine incision requiring re-operation and blood transfusion. Coumadin was restarted following delivery, and both the patient and her babies are now doing very well.

Discussion

Although menstrual irregularity is common in women with chronic liver disease, normal menstrual and ovulatory function resumes in the majority of women following successful liver transplantation (Cundy et al., 1990; de Koning and Haagsma, 1990; Laifer and Guido, 1995, Mass et al., 1996). Most of these women can expect to resume reasonably normal lives post-transplantation; therefore, it is likely that some will entertain the possibility of pregnancy. Of the many reports of successful pregnancy in liver transplant patients in the literature, it seems that the vast majority were conceived spontaneously.

In men with chronic renal failure on dialysis, impaired spermatogenesis and steroidogenesis, particularly elevated luteinizing hormone and reduced testosterone, have been well documented. In most cases, hormonal parameters become normal, and semen quality improves following successful renal transplantation (Prem et al., 1996; Baker, 1998; De Celis and Pedron-Nuevo, 1999). Damage to the pelvic portion of the vas deferens associated with renal transplantation has been reported, resulting in obstructive azospermia (Baker, 1998).

Management of ovulatory dysfunction, tubal or severe male factor infertility in this patient population, with the use of artificial reproductive technologies, has not been addressed in the literature. It is important, however, to be aware of this unique group of patients and the potential problems they present.

Before making the decision to offer artificial reproductive technologies to these patients, it is often necessary, if not essential, to consult other specialists. The patient herself should be made fully aware of the potential risks associated with pregnancy and the use of artificial reproductive technologies, in order to give appropriate informed consent. All patients should undergo preconceptual counselling with a perinatologist experienced with pregnancies in transplant patients, in order to assess the patient’s physical fitness for pregnancy, and/or to optimize her health prior to conception. This may be as simple as the addition of a folic acid supplement, or may involve treatment of comorbid medical problems (e.g. hypertension), or the discontinuation of potentially teratogenic medications, with the substitution of other safer ones. Most commonly used immunosuppressant medications such as prednisone, cyclosporine and azathioprine appear to be relatively safe to use in pregnancy (Albengres et al., 1997; Casele and Laifer, 1998; Ghondour et al., 1998). Consultation with the patient’s transplant specialist may also be useful in this circumstance. In the case of a heritable disease, a genetics consultation is appropriate.

Some liver transplant recipients may be at increased risk for thrombosis, as was the case with our patient who underwent her transplant due to Budd–Chiari syndrome. Consultation with a haematologist is helpful, since most of these patients will require lifelong anticoagulation. This raises two issues for the patient contemplating pregnancy through artificial reproductive technologies. First, coumadin is teratogenic (Cunningham et al., 1993), and is therefore contra-indicated in pregnancy. The second issue relates to the risk of bleeding during procedures, in this case, during transvaginal oocyte retrieval. Both of these issues can be managed by discontinuing the patient’s coumadin, and switching her over to low molecular weight heparin, a once-daily injection that is safe to use in pregnancy. Because the anticoagulant effects of low molecular weight heparin are virtually gone after 24 h (Rosenberg, 1997), it can be discontinued 24–48 h prior to egg retrieval, then restarted 24 h following, in order to minimize the risk of procedure-related bleeding. Calcium supplementation is advis-
able due to the risk of osteoporosis associated with prolonged heparin use. The potential increased thrombosis risk due to supraphysiological concentrations of oestrogen is minimal in the anticoagulated patient.

Once the patient has been medically cleared for pregnancy, ovulation induction can be carried out routinely with the use of GnRH agonists initially for cycle suppression, followed by gonadotrophins. In the case of a liver transplant, the location of the transplant does not pose a problem for oocyte retrieval. Special care should be taken to avoid ovarian hyperstimulation, with its resultant fluid and electrolyte imbalances. It is probably also advisable to be conservative with the number of embryos transferred to avoid the risk of a high-order multiple pregnancy, in an already high-risk medical condition.

The desire for pregnancy is likely to become more common among liver transplant recipients of reproductive age. With careful evaluation and monitoring, and the involvement of appropriate consultants, the use of artificial reproductive technologies may be safely considered in such couples experiencing infertility.

References

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