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First Irish pregnancies after IVF with gestational carrier

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Abstract:

In this report, our early experience with screening, monitoring and coordinating IVF utilising gestational carrier treatment is described. Although congenital and iatrogenic etiologies for uterine factor infertility manifest distinctly different reasons for considering a gestational carrier approach, we outline a unified management strategy for both conditions. One patient had congenital absence of the uterus and proximal vagina (Mayer-Rokitansky-Küster-Hauser syndrome variant), while another patient presented posthysterectomy and adjuvant brachytherapy for invasive squamous cervical carcinoma. Conception was established for both patients, the first pregnancies to be achieved using an IVF/gestational carrier technique in Ireland. As demonstrated here, selected patients with at least one intact ovary who suffer from uterine factor infertility can be excellent candidates for IVF with embryo transfer to a carefully screened gestational carrier. The role of individual and group counselling is reviewed; professional legal advice is prudent in complex cases.

Introduction:

Increased access to the advanced reproductive technologies has enabled a coordinated treatment sequence whereby a woman without a uterus has the potential to use her own gametes to create genetically-related embryos, which may then be transferred to a surrogate host with a functional uterus (a gestational carrier). Although the successful application of this technology only emerged in modern times, the closely allied concept of surrogacy is recorded near the dawn of written history¹. While the unfortunate diagnosis of absent or dysfunctional uterus can exist in several pathological settings, for the reproductive endocrinologist the clinical approach is fairly consistent as described here.

Case 1

A 29 year old non-smoking Caucasian nulligravida with a prior diagnosis of node-positive squamous carcinoma of the cervix (stage IB) sought reproductive endocrinology consultation with her husband. In otherwise good general health, the patient already had surgery and was under the care of a gynaecologic oncologist in preparation for further therapy. The patient wished to begin fertility treatment quickly to "save the eggs, if we can". The husband's semen analysis and laboratory tests were all normal. In coordination with the oncology team, our centre recommended immediate screening in advance of controlled ovarian hyperstimulation for IVF. However, this would be followed by empiric cryopreservation of all embryos with a view to perform embryo transfer only after all adjuvant radio- and/or chemotherapy had concluded and oncology clearance had been obtained. The embryo transfer would then be performed on the patient's sister, who volunteered to carry the pregnancy.

The patient and her partner agreed with and understood this rationale for treatment, designed to maintain fertility potential without compromising effectiveness of her cervical cancer treatment. The sister (age 25) was in good general health, did not smoke, took no regular medications, and had a four year-old son of her own. Screening commenced on her in parallel with legal consultations to develop a "surrogacy contract" protecting the interests of all parties concerned. Individual and group counselling was also undertaken with an emphasis on the procedure itself, the possible outcomes, including the likelihood of treatment failure (i.e., no pregnancy or miscarriage), and the

impact these outcomes might have on the lives of all involved. Written informed consent was obtained from all parties.

Baseline vital signs were normal. Blood type was O positive, rubella immunity was confirmed, and all STD serologies were negative. Pituitary downregulation was achieved with intranasal buserelin (400mcg t.i.d.). No oral contraceptive pills were used. Ovulation induction followed a combined 225IU FSH + 75IU hMG/day regimen, as reported previously². A total of 2100IU gonadotropins was consumed during stimulation, retrieving ten oocytes after a seven day follicular recruitment phase. Oocyte quality was poor; only one 2pn embryo was suitable for cryopreservation after conventional insemination. Two days later, the patient returned to her oncologist to begin brachytherapy. For the sister, all laboratory tests, a saline sonogram and trial embryo transfer were completed over the next 10 months. Approximately one year after the initial single embryo was frozen, the carrier (sister) returned for planned FET. Unfortunately the single cryopreserved embryo did not survive thaw, thus no transfer was done. Because of the intervening adjuvant oncology therapy sustained by the patient (now disease-free for 12 months), it was not recommended that further ovulation induction cycles be performed using her native oocytes.

Soon afterward the sister again proposed her assistance, although going forward she volunteered to be the gestational carrier as well as known oocyte donor for the commissioning couple. Further counselling was mandatory as informed consent was again obtained from the patient, her husband and sister. Ovarian reserve testing confirmed the suitability of the sister to serve as an oocyte donor, and further psychological clearance was obtained. Formal contracts describing the revised treatment were reconfigured with input from solicitors. For the sister (donor-carrier), her pituitary downregulation was accomplished with low-dose oral contraceptives plus intranasal buserelin (400mcg t.i.d.). A total of 3375IU of gonadotropins were used as a combined hMG/FSH protocol. Ovarian morphology was used to determine cycle response and serum E2 levels were not measured.

After a nine day monitored ovulation induction phase, 12 oocytes were retrieved and the following day a 30-day course of 400mg/day intravaginal cyclogest (Actavis Ltd; Devon, UK) with 50mg/day I.M. gestone (Ferring Inc; Dublin, Ireland) was initiated. Seven oocytes advanced to 2pn stage after conventional insemination, and the gestational carrier returned for a twoblastocyst transfer on day five. Three blastocysts were of sufficient quality for cryopreservation. The carrier had a positive qualitative hCG test 12 days after embryo transfer, and a twin (dichorionic) intrauterine pregnancy was confirmed on transvaginal sonogram approximately 20 days later. Healthy twins (male/female) were delivered at 36 weeks gestation by Caesarean, and were discharged from hospital to the commissioning mother and father after four days.

Case 2

A 31 year old non-smoking Caucasian nulligravida with primary amenorrhea presented with her husband for fertility treatment. Both were in good general health and had no medical complaint. Although the diagnosis of Mayer-Rokitansky-K[^]...ster-Hauser syndrome was made during an earlier evaluation for delayed menarche, this was subsequently refined to include unilateral (left) ovarian agenesis and absent left kidney. She had no gross skeletal, cardiac or otic defects. Serum FSH, E2, and P4 (random) were 6.0mIU/ml, 393 pmol/L, and 23 nmol/L respectively. TSH and prolactin were normal. The patient had considered vaginoplasty six years earlier, and a normal 46,XX karyotype was confirmed during that evaluation. She had a satisfactory response to a graduated vaginal dilator

programme, but abandoned this for personal reasons. She also declined consultation for neovaginal surgery when she became sexually active. At our centre, physical examination revealed a well-developed phenotypic female although the vaginal canal ended in a blind pouch and was slightly shortened. No cervix was present and only the right ovary was visualised on transvaginal sonogram. Vital signs were normal. Blood type was B positive, rubella immunity was confirmed, and all STD serologies were negative.

The husband (age 29) was a non-smoker and had never commissioned a pregnancy with any prior partners; his laboratory tests were all normal. Semen analysis showed an overall sperm concentration of 24 million/ml, 58% motility, and normal forms morphology >10% (WHO criteria, 1992). The wife's sister (age 38) suggested herself as a gestational carrier. The sister was a non-smoker, in good general health, and had two biological children of her own conceived without medical assistance. After individual and group counselling, the patient elected to proceed with controlled ovarian hyperstimulation and IVF, with her sister undergoing embryo transfer. A saline-infusion sonogram was performed on the sister and confirmed normal intrauterine contours. All laboratory tests on the sister were normal. Given the limited ovarian reserve usually associated with unilateral absence of the ovary, the likelihood of cycle cancellation due to poor follicular response was acknowledged. Use of donor gametes was declined, however.

Written informed consent was obtained from all parties, and a gestational carrier contract was executed. Since the patient had no uterus and therefore could not menstruate, cycle day determinations using conventional methods were impossible. A commercially available urinary LH test kit was used every other day to determine day of ovulation, and low-dose OCPs were started approximately 14 days after detection of surge. Intranasal buserelin (400mcg t.i.d.) was started on OCP day 12 to complete pituitary downregulation. Follicular recruitment followed a combined FSH/hMG regimen, with a total of 5100IU of gonadotropin consumed over a 12 day stimulation interval. Cycle response was monitored via ovarian morphology only; no serum E2 levels were obtained. Ovulation was induced via 10,000IU hCG administered subcutaneously³ with transvaginal sonogram-guided oocyte retrieval performed 36 hours later. A total of six oocytes were collected (all from R ovary). Four oocytes advanced to the 2pn stage after conventional insemination and all progressed to blastocyst by day 5 in culture. All four blastocysts were cryopreserved to facilitate embryo transfer with the gestational carrier.

Eight weeks later, two blastocysts were thawed and the carrier underwent a two-blastocyst FET under direct transabdominal ultrasound guidance. 400mg intravaginal cyclogest (Actavis Ltd; Devon, UK) with 50mg I.M. gestone (Ferring Inc; Dublin, Ireland) x 30 days was given for luteal support beginning one week prior to embryo transfer. A qualitative hCG test was scheduled for 12 days after transfer. All progesterone was discontinued when a negative pregnancy was registered. Three months later using an identical embryo transfer and supplementary progesterone protocol, the carrier underwent another FET for the two remaining blastocysts. A positive qualitative hCG assay was obtained two weeks later. By cycle day 50, transvaginal sonogram revealed an intrauterine twin (dichorionic) pregnancy and both sacs demonstrated positive cardiac action. Now in the second trimester, the twin pregnancy continues with an uncomplicated obstetrical course.

Discussion

Before the arrival of the advanced reproductive technologies, the dream to achieve a pregnancy by women with intact ovaries but absent uterus could never be realised. More than 20 years ago, the first livebirth from IVF followed by embryo transfer to a gestational carrier was reported⁴ and several centres have presented their experience with this treatment since then⁵⁻⁹. While most clinics have the technical capacity to offer gestational carrier treatments, this highly coordinated therapy constitutes only a small number of cycles even in the busiest IVF programmes¹⁰. Gestational surrogacy is lawfully permitted only in a few European countries¹¹. Although legal in Ireland for several years, its clinical deployment here awaited assent from the RCPI's Institute of Obstetricians & Gynaecologists, which came in 2006. The IVF patients presented in the current report embarked on treatment shortly thereafter, and are believed to be the first in Ireland to conceive using this treatment.

Select patients presenting with gonadal function but no uterus may be offered IVF utilising native oocytes with gestational carrier treatment. However, our two cases brought still further challenges as ovarian reserve was limited either by unilateral ovarian agenesis or by the negative impact of radiotherapy (for cervical carcinoma). The patients were counselled about the significance of impaired ovarian reserve and advised that their risk of cycle cancellation would be increased. Our patient who underwent radiation therapy for malignancy had a sister who served as her gestational carrier and also ultimately provided gametes (after an initial IVF attempt using the patient's own eggs had failed). In this circumstance, since the sister was both oocyte donor and gestational carrier, additional counselling and a highly detailed informed consent developed by an experienced solicitor were indicated. These pregnancies (and healthy twin delivery, in one case) represent a meaningful remedy to the challenges of family building encountered by women without a functional uterus. Notwithstanding the spectrum of etiologies resulting in this unusual condition, the cases described here illustrate how IVF with a gestational carrier approach can serve as a therapeutic pathway to accomplish conception.

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