Human Reproduction vol.15 no.5 pp.1075–1078, 2000

Fifteen years experience with an in-vitro fertilization surrogate gestational pregnancy programme

James M.Goldfarb[1,2,3], Cynthia Austin[1,2], Barry Peskin[1,2], Hannah Lisbona[1,2], Nina Desai[1,2] and J.Ricardo Loret de Mola[1,2]

[1]Department of Reproductive Biology, Case Western Reserve University School of Medicine and [2]Department of Obstetrics and Gynecology, University MacDonald Women's Hospital, University Hospitals of Cleveland, Cleveland, Ohio, USA

[3]To whom correspondence should be addressed

The purpose of our study was to review and evaluate retrospectively the experience of an in-vitro fertilization (IVF) surrogate gestational programme in a tertiary care and academic centre. In a 15 year period from 1984 to 1999, a total of 180 cycles of IVF surrogate gestational pregnancy was started in 112 couples. On average, the women were 34.4 ± 4.4 years of age, had 11.1 ± 0.72 oocytes obtained per retrieval, 7.1 ± 0.5 oocytes fertilized and 5.8 ± 0.4 embryos subsequently cleaved. Sixteen cycles (8.9%) were cancelled due to poor stimulation. Except for six cycles (3.3%) where there were no embryos available, an average of 3.2 ± 0.1 embryos was transferred to each individual recipient. The overall pregnancy rate per cycle after IVF surrogacy was 24% (38 of 158), with a clinical pregnancy rate of 19% (30 of 158), and a live birth rate of 15.8% (25 of 158). When compared to patients who underwent a hysterectomy, individuals with congenital absence of the uterus had significantly more oocytes retrieved ($P < 0.006$), fertilized, cleaved and more embryos available for transfer despite being of comparable age. IVF surrogate gestation is an established, yet still controversial, approach to the care of infertile couples. Take-home baby rates are comparable to conventional IVF over the same 15 year span in our programme. Patients with congenital absence of the uterus responded to ovulation induction better than patients who underwent a hysterectomy, perhaps due in part to ovarian compromise from previous surgical procedures.

Key words: congenital absence of the uterus/gestational carrier/hysterectomy/in-vitro fertilization/surrogate mother

Introduction

A new obstetric paradigm has emerged as a result of infertile couples pursuing additional options for producing biologically related children. The use of these services continues to be on the rise, and as certain states and countries raise barriers against such arrangements, many more couples look to the USA desperately seeking assistance.

Traditional surrogacy is defined as a woman who contracts with a couple to be artificially inseminated with the husband's semen, carry a pregnancy, and after delivery relinquishes the child and all paternal rights to the commissioning parents (Benshushan *et al*., 1997). Surrogate gestational carriers are significantly different, since the surrogate has no genetic link to the fetus. The pregnancy is conceived by using the infertile couple's gametes and the embryos obtained are then transferred to the surrogate's uterus after it has been prepared hormonally to carry such a pregnancy. Both methods of surrogacy are controversial and have been criticized by segments of the media and the medical establishment. However, surrogacy continues to be a very acceptable option for many infertile couples. We reported the first successful surrogate gestational pregnancy after IVF in 1985 (Utian *et al*., 1985). Four years later we published the results of our first series of 39 cycles of surrogate gestational transfer after IVF from women who did not have a functional uterus (Utian *et al*., 1989). The results from that study revealed a pregnancy rate of 18% per egg recovery.

The purpose of this report is to provide a 15 year follow-up of our experience with such a programme, outline our current protocols, describe subsequent outcomes and results, and to make some general recommendations for other infertility care-givers.

The remarkable changes seen with the most recent developments in IVF, along with more accepted social and ethical attitudes towards procreation using all forms of third-party assisted reproduction are now making this treatment modality more widely accepted. This will allow couples with multiple infertility causes such as genetic aberrations, absence of the uterus, as well as repetitive ovulation induction, IVF and ovarian failure an opportunity to conceive. The high successes achieved with our current technology and the possibility of having a genetically related offspring continues to encourage the use of IVF surrogacy.

Materials and methods

The Ethics Committees at Mount Sinai Medical Center (1982–1989) and University Hospitals of Cleveland (1990–present) (Cleveland, OH, USA) reviewed all our protocols for the use of surrogate gestational carriers. Approval has thus been in existence throughout the duration of the programme. This retrospective study covers all patients admitted into our programme from 1984 through 1999, during which time a total of 180 cycles of IVF surrogacy was performed in 112 couples. The women were 34.4 ± 4.4 years of age, with a parity of 0.2 ± 0.6. Of these patients, 11 came from abroad for their care (9.8%), and 101 were from the USA (90.2%). Fifty-one women had undergone hysterectomies for a variety of conditions; 15 had congen-

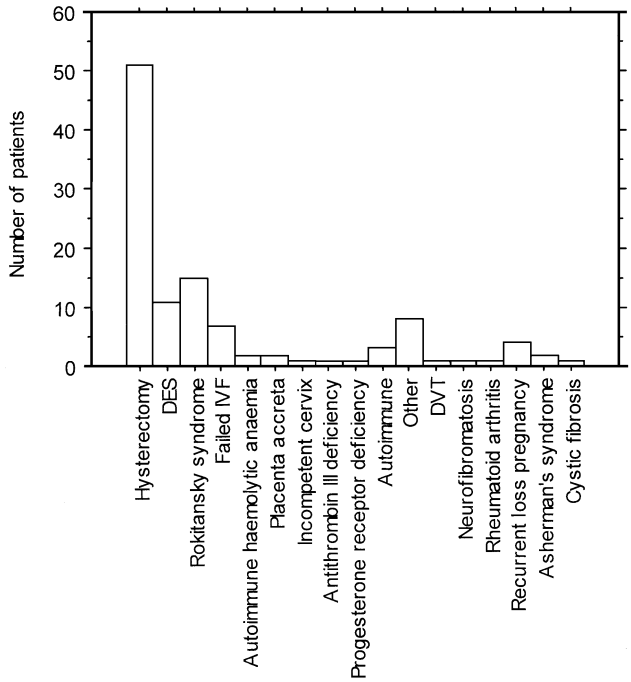

Figure 1. Diagnostic groups of patients entering the IVF surrogacy programme. DES = diethylstilboestrol; DVT = deep vein thrombosis.

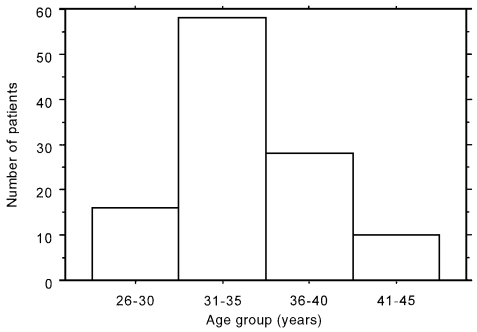

Figure 2. Age distribution of patients entering the IVF surrogate programme.

ital absence of the uterus (Mayer–Rokitansky–Kuster–Hauser syndrome), and the remaining 46 patients had a variety of indications (Figure 1). Their age distribution can be seen in Figure 2.

Gestational carriers

Recruitment of gestational carriers was carried out by patients and their partners, and many of them were assisted by various agencies. In 14 couples, a relative served as the host mother of the commissioning couple. All of our couples were married. Care was taken in every instance to assure that the host's partner was in complete support of the proposed plan of treatment. Furthermore, an independent psychologist carried out a detailed psychological assessment of all parties to the arrangement, and submitted the findings to the IVF team for a final decision on their suitability.

Ovulation induction and IVF

A long protocol of pituitary desensitization was used (and is currently in use), starting in the luteal phase of the menstrual cycle, both in the commissioning mother and the host mother, in order to synchronize them for the IVF cycle. This was done by daily injections of luprolide acetate (Lupron, TAP Pharmaceuticals, Inc., Dearfield, IL, USA), s.c. at 0.5 mg daily. The date of ovulation was determined in both patients using a combination of ovulation predictor kits, as well as basal body temperature charts to determine the LH surge, and pituitary desensitization was started a week later. Other approaches, such as weekly progesterone measurements or oral contraceptives, have been described in order to initiate pituitary desensitization in a timely fashion (Batzer *et al*., 1992; Ben-Rafael *et al*., 1998). A transvaginal ultrasound was carried out, both in the commissioning and the host mother, along with serum oestradiol determination to assure proper suppression. The commissioning mother was then started on daily injections of human menopausal gonadotrophins, at 225–300 IU daily, and the dose was adjusted according to ovarian response, which was monitored with transvaginal ultrasound scanning and serum oestradiol concentrations. Once two leading follicles measuring $\geqslant$18 mm in diameter were observed by ultrasonography, 10 000 IU of human chorionic gonadotrophin (HCG) were administered to the commissioning mother, and a transvaginal ultrasound-guided oocyte retrieval was performed 36 h later under i.v. sedation. The surrogate host mother was started on oral oestradiol valerate on an escalating dose, starting at 2 mg/day, to 6 mg/day to initiate on the same day that the ovulation induction was started in the commissioning mother. Regular ultrasound scanning for endometrial thickness was begun a week later, and was used to determine the need for modifying the oestrogen replacement strategy. Intramuscular progesterone in oil, or vaginal administration of natural progesterone suppositories, at a dose of 100 mg a day was added to the drug regimen of the host mother, starting on the day after HCG administration. The hormone replacement therapy of the host mother was continued until 12 weeks gestation if embryo implantation and development had occurred. Standard techniques for IVF (n = 160 cycles), intracytoplasmic sperm injection (ICSI) (n = 3 cycles), or subzonal sperm injection (n = 1 cycle), were utilized in patients for whom oocyte retrieval had been successful. Sixteen cycles were cancelled due to poor stimulation. Six cycles had no embryos available for transfer. We transferred two to four embryos in most of our patients (range one to six embryos). A serum β-HCG measurement was carried out 12 days after embryo transfer, and host mothers with positive results had ultrasound scanning 2 weeks later for detection of fetal sacs, and subsequently a week later, for the detection of fetal heart activity and confirmation of zygosity.

Statistical analysis

The medical records were retrospectively used to obtain information relevant to this study and data were entered into an IBM personal computer 300 PL. The database was set up and analysis done using a statistical package from Abacus Software Concepts (StatView 4.5, Berkeley, CA, USA). The data are presented as mean ± SEM. For evaluating the differences between patients grouped by different diagnosis, the data were assessed by analysis of variance (ANOVA), and when a significant F-ratio was defined, groups were compared using Fisher's post-hoc test. Values of $P < 0.05$ were considered significant.

Results

There were 11.1 ± 0.72 oocytes retrieved in our patients, 7.1 ± 0.5 oocytes fertilized, and 5.8 ± 0.4 embryos cleaved to the 2-cell stage. On average, 1.3 ± 0.3 embryos were frozen at the pronuclear stage, 3.2 ± 0.1 embryos were transferred, and 0.54 ± 0.16 embryos were frozen at the blastocyst stage. Sixteen of 180 cycles were cancelled due to poor ovarian response (8.9%), and in six additional cycles (3.3%) no

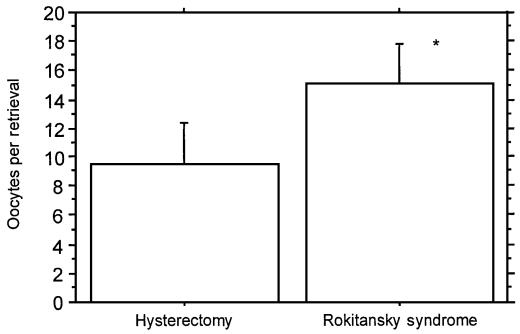

Figure 3. Comparison of oocytes obtained per retrieval between hysterectomy and Rokitansky syndrome patients; $*P < 0.006$.

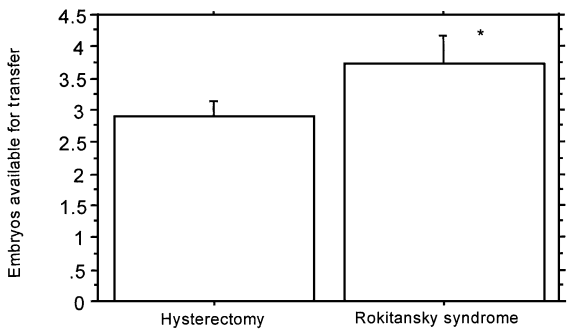

Figure 4. Comparison of embryos available for transfer between hysterectomy and Rokitansky syndrome patients; $*P < 0.01$.

Table I. Pregnancy outcome by age group for the IVF surrogacy programme

	Age (years)				Totals
	26–30	31–35	36–40	41–45	
Singleton	9	6	2	1	18
Twins	2	2	1	1	6
Triplets	0	1	0	0	1
Not pregnant	10	55	39	16	120
Cancelled cycle	2	11	2	1	16
Miscarriage	3	0	1	0	4
Chemical pregnancy	3	1	4	0	8
Cancelled transfer	1	4	1	0	6
Ectopic pregnancy	0	1	0	0	1
Totals	30	81	50	19	180

embryos were available for transfer. The overall pregnancy rate after IVF surrogacy was 38/158 (24%), with a clinical pregnancy rate of 30/158 (19%), and a live birth rate of 25/158 (15.8%). Table I presents all the data by age group and pregnancy outcome.

When compared to patients who underwent a hysterectomy ($n = 51$), individuals with congenital absence of the uterus ($n = 15$; Mayer–Rokitansky–Kauster–Hauser syndrome), had more oocytes retrieved (9.43 ± 1.4 compared with 15 ± 1.2 oocytes per retrieval respectively; $P < 0.006$) (Figure 3); and more mature oocytes (4.5 ± 0.7, compared to 9 ± 0.8 oocytes per retrieval, respectively) ($P < 0.01$). There were more oocytes fertilized ($P < 0.001$), cleaved to the 2-cell stage ($P < 0.01$), and embryos available for cryopreservation at the pronuclear stage ($P < 0.01$) in the Rokitansky syndrome group (data not shown). More embryos were available for transfer in Rokitansky syndrome patients ($P < 0.01$) (Figure 4), despite having comparable ages to hysterectomy patients (32.4 ± 0.8 and 33.2 ± 0.4 years respectively) (not significant).

Discussion

This study is one of the largest experiences published to date on gestational surrogacy (Reame *et al*., 1990; Marrs *et al*., 1993; Parkinson *et al*., 1998). Pregnancy rates are comparable to conventional IVF cycles over the same 15 year period in our programme (J.M.Goldfarb and J.R.Loret de Mola, unpublished observations). It also reveals a variable response to ovulation induction in women born without a uterus, as compared with patients who have a hysterectomy. These patients had more oocytes retrieved and more embryos available for transfer than patients who underwent a hysterectomy, perhaps due in part to ovarian vascular compromise from previous surgical procedures. We infer this based on the fact that the patients' ages were comparable between the two groups. Unfortunately, we do not have day 3 FSH concentrations or clomiphene challenge tests to support this claim. This unexpected finding became evident due to the large number of patients seen in our programme over the 15 year period, and is different from previous reports in the literature (Corson *et al*., 1998). We believe that this is an important finding that should be addressed during patient counselling, i.e. for patients to have realistic pregnancy expectations after undergoing a hysterectomy.

Other factors also observed in our study included an expected decrease in the oestradiol concentrations, number of oocytes retrieved, and pregnancy rates as women aged (data not shown). A recent study (Meniru and Craft, 1997) initially addressed some of the issues of hysterectomy and surrogacy. In their study, they discussed the possibility that different hysterectomy techniques could affect the outcome of surrogacy. However, the three women in their study who had a radical hysterectomy responded favourably to ovulation induction, and their respective host mothers became pregnant. They were unable to show whether this was related to the age of the commissioning mothers since they were all under 30 years of age, and most of the failures in their programme could be linked to the commissioning mother's age. We did not experience any technical difficulties or excessive vaginal bleeding after oocyte retrieval in patients with Rokitansky syndrome (Batzer *et al*., 1992; Ben-Rafael *et al*., 1998).

We believe that gestational surrogacy is worth considering in women who have lost their uterus, were born without a uterus, have had repeated failures at implantation from a variety of sources, or have an underlying medical condition that prevents them from being pregnant. Our experience with this procedure has been extensive, and the process of IVF surrogate pregnancy has thus, so far, been uncomplicated and gratifying. This procedure offers hope for couples to produce their own genetic family. Perinatal and obstetric outcomes in patients undergoing surrogacy are also reassuring (Parkinson *et al*., 1998). We believe that this form of infertility treatment is now well established with a proven track record, and we

endorse its continuation. Nonetheless, we believe that all programmes involved in this type of arrangement should adopt strict guidelines (Keane and Breo, 1981; Utian *et al*., 1989; Batzer *et al*., 1992), with direct evaluation and monitoring of all the procedures involved in the care of these patients. We have previously published detailed guidelines (Utian, *et al*., 1989) regarding this matter, and our strict adherence to them has been associated with gratifying experiences to date. We should continue to monitor not only the medical issues regarding these couples, but also the ethical and legal matters which must be assessed continuously, given the ever-changing medical/legal environment in the USA. Finally, long-term psychological follow-up and documentation of findings, both positive and negative, is of great importance in the continuing evaluation these types of procedures and arrangements.

References

Batzer, F.R., Corson, S., Gocid, B. *et al*. (1992) Genetic offspring with vaginal agenesis: specific medical and legal issues. *Am. J. Obstet. Gynecol*., **167**, 1288–1292.

Ben-Rafael, Z., Bar-Hava, I., Levy, T. and Orvieto, R. (1998) Simplifying ovulation induction for surrogacy in women with Mayer–Rokitansky–Kauster–Hauser syndrome. *Hum. Reprod*., **13**, 1470–1471.

Benshushan, A. and Schenker, J.G. (1997) Legitimizing surrogacy in Israel. *Hum. Reprod*., **12**, 1832–1834.

Corson, S., Kelly, M., Braverman, A.M. and English, M.E. (1998) Gestational carrier pregnancy. *Fertil. Steril*., **69**, 670–674.

Keane, N.P. and Breo, D.L. (eds) (1981) *The Surrogate Mother.* Everest House, New York.

Marrs, R.P., Ringler, G.E., Stein, A.L. *et al*. (1993) The use of surrogate gestational carriers for assisted-reproductive technologies. *Am. J. Obstet. Gynecol*., **168**, 1858–1863.

Meniru, G.I. and Craft, I.L. (1997) Experience with gestational surrogacy as a treatment for sterility resulting from hysterectomy. *Hum. Reprod*., **12**, 51–54.

Parkinson, J., Tran, C., Tan, T. *et al*. (1999) Perinatal outcome after in-vitro fertilization–surrogacy. *Hum. Reprod*., **14**, 671–676.

Reame, N.E. and Parker, P.J. (1990) Surrogate pregnancy: clinical features of forty-four cases. *Am. J. Obstet. Gynecol*., **162**, 1220–1225.

Utian, W.H., Sheehan, L., Goldfarb, J.M. and Kiwi, R. (1985) Successful pregnancy after in-vitro fertilization–embryo transfer from an infertile woman to a surrogate. *N. Engl. J. Med*., **313**, 1351–1352.

Utian, W.H., Goldfarb, J.M., Kiwi, R. *et al*. (1989) Preliminary experience with an in-vitro fertilization–surrogate gestational pregnancy. *Fertil. Steril*., **52**, 633–638.

Received on October 12, 1999; accepted on January 20, 2000