Article

# Eight years' experience with an IVF surrogate gestational pregnancy programme

Dr Arieh Raziel is a clinician at Assaf Harofeh Medical Centre affiliated to Tel-Aviv University. He is responsible for the andrology clinic and sperm bank at this hospital and is an active participant in the IVF unit. His special interests are in recurrent pregnancy loss and the surrogacy programme. Dr Raziel received his MD in 1982, his Master's degree in 1990 and specialization in 1991. He is also Tel-Aviv University co-ordinator for the national examinations in Obstetrics and Gynecology.

*Dr Arieh Raziel*

Arieh Raziel[1], Morey Schachter, Deborah Strassburger, Dafna Komarovsky, Raphael Ron-El, Shevach Friedler
Infertility and IVF Unit, Assaf Harofeh Medical Centre, Tel-Aviv University,
Zerifin, 70300, Israel
[1]Correspondence: Tel: +972 8 9779005; Fax: +972 8 9779003; e-mail: araziel@012.net.il; araziel@asaf.health.gov.il

## Abstract

The aim of this study was to retrospectively audit eight years' experience of an IVF surrogate gestational programme and to compare the outcome of surrogacy due to absence of the uterus with surrogacy indicated for repeated IVF failure and recurrent abortions. A total of 60 cycles of IVF surrogate pregnancy were initiated in 19 treated couples. Absence of the uterus was the indication for surrogacy in 10 cases: Rokitansky syndrome (eight cases) and post-hysterectomy (two cases) designated as group A. The indications in the remaining nine patients (group B) were: IVF implantation failure (three cases), habitual abortions (four cases) and deteriorating maternal diseases (two cases). IVF performance and subsequent pregnancy outcome of groups A and B were compared. There was no difference in ovarian stimulation parameters and in IVF performance between the groups A and B. The overall pregnancy rate per transfer was 10/60 (17%). The pregnancy rates per patient and per transfer were 7/10 (70%) and 7/35 (20%) in group A compared with 3/9 (33%) and 3/25 (12%) in group B. A median number of three treatment cycles were needed to achieve pregnancy. In conclusion, the existence or absence of the uterus in the commissioning mothers is irrelevant for their IVF performance and conception rates. In patients who conceived after more than three IVF cycles, an additional 'oocyte factor' might be present.

***Keywords:*** *gestational carrier, in-vitro fertilization, Rokitansky syndrome, surrogate mother*

## Introduction

Traditional or 'natural' surrogacy is defined as where a couple contracts with a woman to be artificially inseminated with the husband's semen, carry the pregnancy and after delivery give the child and all parents' rights to the commissioning couple. In 'full' surrogacy, the infertile couple's gametes and the embryos obtained are transferred to the surrogate's uterus to carry such a pregnancy. The surrogate gestation carrier has no genetic link to the fetus. Both types of surrogacy have raised many ethical questions and are therefore controversial.

Arguments have been raised against commercial surrogacy, claiming exploitation of the surrogates. The gestation carriers have been considered by some as a 'womb to rent'. Comparisons have been made between commercial surrogacy and organ transplant marketing. Gestation surrogacy has even been described as a form of 'slavery' (Wilkinson, 2003). Despite all these thoughts, surrogacy has become an established method for producing biologically related children. Surrogacy is a solution for women born without a uterus (Beski *et al.*, 2000) and women without a uterus for various gynaecological and obstetric pathologies (Meniru and Craft, 1997). Other major indications for surrogacy are repeated reproductive failure after IVF–embryo transfer treatment (both implantation failure and pregnancy loss), for which the exact diagnostic criteria have never been established. Another group of patients are those with a pre-existing disease, which may greatly worsen during pregnancy.

The first reported case of a successful IVF surrogate pregnancy was by Utian *et al.*, in 1985. This group further

published their extended experience (Goldfarb *et al.*, 2000). Other groups in Britain (Brindsen *et al.*, 2000), Australia (Stafford-Bell and Copeland, 2001) and Finland (Soderstrom-Anttila *et al.*, 2002), published their local experience in IVF surrogacy. Woodward *et al.* (2004) recently described the birth of healthy twins, following surrogacy involving a female patient's biological mother as surrogate, using anonymous donated embryos. The legal side of adoption took over 3 years to complete, emphasizing the ever-widening gap between artificial reproductive technology and laws governing the technology.

The aim of this study was to evaluate retrospectively eight years' experience of an IVF surrogate gestational programme in one tertiary care and academic centre.

Experience with 60 IVF cycles of IVF surrogacy was reviewed. Further, the variables of surrogate mothers without a uterus were compared with those of mothers with a functional uterus (suffering from recurrent abortions and implantation failure).

## Guidelines for surrogacy in Israel

State-controlled surrogacy has been legislated in a very few countries around the world. In Israel, it represents a compromise between orthodox and liberal approaches (Benshushan and Schenker, 1997). The new surrogacy law in Israel has been valid since March 1996 (Frenkel, 2001). A multidisciplinary committee must approve every case of surrogacy. The committee includes: a gynaecologist, an internal medicine physician, a clinical psychologist, a social worker, a clergyman and a lawyer as public representatives. Only full surrogacy is permitted. Both partners of the commissioning couple should provide the gametes. Sperm donation is not allowed. Ovum donation is allowed as an exception, with the approval of the committee. The parties should be adult Israeli citizens to prevent abuse of foreign women without legal residency status. The surrogate mother should be unmarried, single or divorced, with at least one child of her own. She should be anonymous to the commissioning couple to avoid any potential pressure on relatives of the family to become surrogate. The surrogate and the commissioning couple should be of the same religion. The surrogate mother receives a fixed payment for her service. The payments are approved by the committee. An additional sum of money is kept for further expenses such as psychological aid. Surrogacy is restricted to only two deliveries by the same surrogate mother. The child is under the responsibility of a social worker from birth until the moment of completion of an adoption procedure within 7 days from delivery (Honig *et al.*, 2000).

## Materials and methods

The medical records of 19 patients participating in surrogacy gestation that occurred during the years 1997 to 2004, at Assaf Harofeh Medical Centre, Zerifin, Israel, were reviewed (**Table 1**).

Absence of the uterus was the indication for surrogacy in 10 of 19 cases: Rokitansky syndrome (eight cases) and post-hysterectomy (two cases) – group A. Hysterectomy was performed because of bleeding cervical pregnancy in one case and an extremely large fibroid uterus causing menometrorrhagia, in the second patient. The indications for surrogacy in the remaining nine group B patients were: IVF implantation failure (three cases), habitual abortions (four cases) seriously impaired renal function post-renal transplantation in one patient, and an endangering oestrogen-dependent congenital haemangioma around the area of the neck in one patient. Of these nine patients, three had never conceived. One of the remaining six patients had suffered from 24 consecutive abortions (Raziel *et al.*, 2000), one had suffered from six consecutive abortions, and one had conceived and delivered after 12 IVF trials. On her repeated attempts for a second child she underwent another 12 trials that failed to achieve pregnancy and she was therefore referred to surrogacy. The 'original' female and male gametes were transferred in all cases to the surrogate mother.

The age of the patients, day 3 basal serum FSH and LH values were assessed. Regarding ovarian stimulation: duration of treatment and number of gonadotrophin ampoules needed for stimulation, hormonal profile (oestradiol, progesterone), number of follicles, aspirated oocytes, and total number of developing and transferred embryos were compared and evaluated.

**Table 1.** Diagnostic group of 19 patients entering the IVF surrogacy programme.

| *Presentation* | *Number of patients* |
|---|---|
| *Group A: congenital and acquired absent uterus* | |
| Rokitansky syndrome | 8 |
| Post-hysterectomy: cervical pregnancy, large fibroids | 2 |
| *Group B: intact uterus and other indications* | |
| Repeated IVF implantation failures | 3 |
| High-order habitual abortions | 4 |
| Maternal disease: post-renal transplantation, oestrogen-dependent haemangioma | 2 |

Ovarian stimulation was carried out by the intramuscular administration of 3.75 mg triptorelin (Decapeptyl; Ferring, Malmo, Sweden) or 600 µg intranasal nafarelin (Synarel; Delpharm, France) two weeks prior to individualized administration of human menopausal gonadotrophins (Menogon; Ferring, Manheim, Germany) or recombinant preparations (Gonal F - Serono, Aubans, Switzerland; Puregon – Organon, Lausanne, Switzerland). For the treatment of patients with Rokitansky syndrome, weekly determination of serum progesterone to identify accurately the luteal phase and thus administer gonadotrophin-releasing hormone (GnRH) analogue preparation was done as suggested by Ben-Rafael *et al.*, 1998. Oocyte retrieval was performed by vaginal route guided by ultrasound under general anaesthesia. The morphology of each of the aspirated oocytes, after denudation with hyaluronidase, was described. Intracytoplasmic sperm injection (ICSI) was carried out in all patients according to the methodology described by Van Steirteghem *et al.*, 1993. It is our rule to perform IVF when possible. As in other IVF units, ICSI is performed when the semen quality of the patient is low on previous failed IVF cycles and in low responders. Since our fertilization rate and embryo quality are often better in ICSI than in IVF (as we see in mixed IVF/ICSI cycles), we prefer to perform ICSI rather than IVF in these unique cases of surrogacy.

Fertilization was confirmed after 16 to 18 h by visualization of two distinct pronuclei. Cleavage was assessed 24 h later. Grade I embryos were defined as embryos in which all blastomeres were of equal size, grade II embryos had blastomeres with unequal or equal size with a maximum of 20% fragments of the embryo volume. In grade III, 20–50% of the volume contained fragmentation and if >50% fragmentation was present, the morphology of the embryo was classed as grade IV. Embryos were considered for transfer and introduced into the uterine cavity 48–72 h after the ICSI procedure. Embryo transfer was performed with a Wallace catheter (Simcare, Lancing, UK).

In order to synchronize the commissioning mother and the surrogate, the latter used oral contraceptives during the pituitary desensitization of the commissioning mother. The surrogate mother was instructed to stop the ingestion of oral contraceptives so she had withdrawal bleeding in parallel with the start of individualized gonadotrophin injection in the commissioning mother.

Pituitary desensitization was not used in the gestational carrier for synchronization. The surrogate mother started daily oral oestradiol valerate in escalating doses, starting at 2 mg/day up to a maximum of 6 mg/day in an individualized fashion. A minimal endometrial thickness of at least 6 mm triphasic endometrium was attained before transfer was attempted. Intramuscular progesterone in oil (Gestone; Paines and Byrne, Surrey, UK) 50 mg per day, or vaginal micronized progesterone (Utrogestan; Besins International Laboratories, Paris, France) 200 mg every 8 h, were added to the surrogate, starting on the human chorionic gonadotrophin (HCG) day of the biological mother. If pregnancy was diagnosed, this combined regimen was continued until 8 weeks of gestation.

Pregnancy rate was calculated considering only clinical pregnancies, determined by the visualization of a gestational sac by transvaginal ultrasound 3 to 4 weeks after embryo transfer. Early abortion was defined as pregnancy loss that took place before 12 weeks of gestation, and a late abortion after 12 and before 20 weeks of gestation.

## Statistical analysis

Results were expressed as means ± SD. Statistical analysis was performed with the JMP statistical package (version 3.2.2.; SAS Institute Inc., Cary, NC, USA) using Student's *t*-test as appropriate. Statistical significance was defined as a value of $P < 0.05$.

# Results

Pertinent clinical data on ovarian stimulation and IVF performance are depicted in **Table 2**.

A mean number of 10 ± 5.2 oocytes were aspirated from the commissioning mothers. Of 494 oocytes, 430 (87%) were mature, 30 (6%) were metaphase I oocytes and those remaining were at the germinal vesicle (1%) and degenerated (6%) stages.

A mean number of 5.3 ± 3.2 embryos were observed, of which a mean number of 2.6 ± 0.9 embryos were transferred. Of 143 embryos, 61 (43%) were 'good' quality (grades I, I–II), 76 (53%) were 'intermediate' quality, and the remaining 4% were bad-quality embryos (grade III or above).

Patients with congenital or acquired absence of the uterus were significantly younger than patients with repeated abortions or repeated IVF trials ($P < 0.001$). Ovarian stimulation and IVF outcomes of those patients are shown in **Table 3**. There was no difference in any of the parameters between the two groups except for a significantly higher mean serum oestradiol concentration on HCG day in group A.

Four patients underwent only one surrogate IVF trial and all of them conceived. Five patients underwent two surrogate IVF cycles. Pregnancy was achieved in one of these patients. Pregnancy was reported in two of another four patients who performed three surrogate IVF cycles. Two patients underwent four surrogate IVF trials without any pregnancy. One pregnancy was achieved in two patients who underwent five surrogate IVF trials. Conception was achieved in another two patients after seven and after nine IVF trials respectively. One surrogate was pregnant twice: the first pregnancy, on the first IVF trial, ended in a missed abortion. The second surrogate IVF pregnancy was after another three successive cycles. It ended in a normal delivery.

The overall pregnancy rate per transfer was 17% (10/60), and a live birth rate of 15% (9/60) per cycle was found. The pregnant patients underwent a median of three treatment cycles. Six of 10 pregnancies were achieved in patients with absence of the uterus.

**Table 2.** Ovarian stimulation and IVF performance of 19 cases in 60 treatment cycles of a surrogate pregnancy programme, during a period of 8 years. Values are means ± SD.

| | |
|---|---|
| Mean age (years) | 33 ± 4.0 |
| FSH (mIU/ml) | 5.1 ± 1.0 |
| LH (mIU/ml) | 5.2 ± 2.1 |
| No. gonadotrophin ampoules | 35 ± 13 |
| No. gonadotrophin days | 11 ± 2.1 |
| Oestradiol on HCG day (pg/ml) | 2692 ± 1627 |
| Progesterone on HCG day (ng/ml) | 1.5 ± 0.6 |
| No. follicles | 11 ± 5.4 |
| No. oocytes | 10 ± 5.2 |
| No. MII oocytes | 8 ± 3.7 |
| No. fertilizations | 5.8 ± 3.3 |
| No. all embryos | 5.3 ± 3.2 |
| No. embryos per transfer | 2.6 ± 0.9 |

HCG, human chorionic gonadotrophin; MII, metaphase II.

**Table 3.** The characteristics and ovarian stimulation outcome of IVF surrogacy cycles – a comparison between different indications for surrogacy: absence of the uterus versus recurrent abortions and repeated IVF failure. Values are means ± SD; NS = not significant.

| | *Group A (n = 35)* | *Group B (n = 25)* | *P-value*[a] |
|---|---|---|---|
| Mean age (years) | 31.2 ± 3.8 | 35.4 ± 3.9 | <0.001 |
| FSH (mIU/ml) | 6.0 ± 2.5 | 5.9 ± 2.2 | NS |
| LH (mIU/ml) | 4.8 ± 2.1 | 5.3 ± 1.9 | NS |
| No. gonadotrophin ampoules | 35.0 ± 11.9 | 35 ± 15.8 | NS |
| No. gonadotrophin days | 12.0 ± 1.3 | 11 ± 2.5 | NS |
| Oestradiol on HCG day (pg/ml) | 3131 ± 1711 | 2342 ± 1628 | 0.04 |
| Progesterone on HCG day (ng/ml) | 1.4 ± 0.7 | 1.5 ± 0.4 | NS |
| No. follicles | 12 ± 4.8 | 10.0 ± 6.3 | NS |
| No. oocytes | 10.6 ± 4.3 | 8.9 ± 6.2 | NS |
| No. MII oocytes | 8.8 ± 3.2 | 6.8.0 ± 4.2 | NS |
| No. fertilizations | 6.5 ± 2.7 | 5.0 ± 3.7 | NS |
| No. all embryos | 5.4 ± 2.7 | 5.2 ± 3.8 | NS |
| No. embryos per transfer | 2.7 ± 0.9 | 2.5 ± 0.7 | NS |

Group A, patients with congenital or acquired absence of uterus; group B: patients with recurrent abortions or repeated failure in IVF.
HCG, human chorionic gonadotrophin; MII, metaphase II.
[a]Student's *t*-test

## Discussion

Despite the fact that surrogacy has become an integral part of infertility management, only few studies have been published concerning IVF surrogacy, the perinatal outcome and follow-up of the children born. Most publications on surrogacy discuss mainly the ethical dilemma and legislation.

The largest recent study published today on gestational surrogacy, among others (Marrs *et al.*, 1993; Serafini *et al.*, 1994; Brinsden *et al.*, 2000) is the one by Goldfarb *et al.*, 2000. This study covered a 15-year period during 1984–1999, and 180 cycles in 112 couples. Although the number of cycles is impressive, IVF procedures changed through these years: the administered drugs, surgical approach, kind of anaesthesia, the skill and media in the IVF laboratory. According to their experience, a mean of 11.1 oocytes were retrieved, 7.1 fertilized, 5.8 cleaved and 3.2 were transferred. These parameters were similar to those in the current series. However, they found a better surrogate IVF performance in

patients with congenital absence of the uterus, as compared with patients post-hysterectomy. This was attributed to the possibility of compromised ovarian vascularity caused by previous surgery. Corson *et al.* in 1998, in another analysis between the years 1988 and 1997 of 77 couples, could not find a difference in the above parameters between congenital absence of the uterus and post-hysterectomy. The mean age of the patients with Rokitansky syndrome was significantly lower among the patients compared with post-hysterectomy, as in the current study. According to the above, the concept that patients with congenital absent uterus respond to ovulation induction better than patients who have undergone hysterectomy remains open for discussion.

The number of patients without a uterus in the present series was relatively low; therefore a comparison between IVF performance in patients with congenital and acquired absence of the uterus was not done. Results in patients without a uterus (mostly congenital and also acquired) were compared with those from IVF surrogacy due to repeated abortions or IVF failures in the commissioning mother. It should be noted that group B included different aetiopathologies, and it would have been more appropriate to compare patients with absent uterus with patients in each of the distinct pathologies. Such a comparison was not possible due to the small number of patients. No difference was found in IVF performance between groups A and B so it can be assumed that the existence or the absence of the uterus is irrelevant to the IVF performance in IVF surrogacy.

The pregnancy rate per transfer was 17% (10/60), and the live birth rate 15% (9/60). These numbers are somewhat low compared with the 'regular IVF programme': pregnancy and live birth rates of 30% and 25.5%, respectively. Similar results were reported by Goldfarb *et al.* (2000): a clinical pregnancy rate of 30/158 (19%) and a live birth rate of 25/158 (16%). However, Corson *et al.*, in 1998 reported a pregnancy rate of 30.8% per cycle, in patients under the age of 40 years, in 117 fresh and cryopreservation cycles. No pregnancy was achieved in patients aged over 40 years, in 27 cycles. Reasons for the low pregnancy rates are unknown. They may be related to different characteristics of the patients such as older age and/or the presence of prominent 'oocyte factor'.

In summary, IVF surrogacy is a well-established treatment in cases of congenital absent uterus, post-hysterectomy and in patients with recurrent abortions or IVF failures. The existence or absence of the uterus was irrelevant to the performance in IVF. The overall pregnancy rate per transfer was 17% (10/60) and a live birth rate of 15% (9/60) per cycle was found. A median of three surrogate IVF cycles is needed to achieve a pregnancy.

## References


Ben-Rafael Z, Bar-Hava I, Levy T *et al.* 1998 Simplifying ovulation induction for surrogacy in women with Mayer–Rokitansky–Kuster–Hauser syndrome. *Human Reproduction* **13**, 1470–1471.

Benshushan A, Schenker JG 1997 Legitimizing surrogacy in Israel. *Human Reproduction* **12**, 1832–1834.

Beski S, Gorgy A, Venkat G *et al.* 2000 Gestational surrogacy: a feasible option for patients with Rokitansky syndrome. *Human Reproduction* **15**, 2326–2328.

Brinsden PR, Appleton TC, Murray E *et al.* 2000 Treatment by in-vitro fertilization with surrogacy: experience of one British centre. *British Medical Journal* **320**, 924–928.

Corson SL, Kelly M, Braverman AM *et al.* 1998 Gestational carrier surrogacy. *Fertility and Sterility* **69**, 670–674.

Frenkel DA 2001 Legal regulation of surrogate motherhood in Israel. *Medicine and Law* **20**, 605–612.

Goldfarb JM, Austin C, Peskin B *et al.* 2000 Fifteen year experience with an in-vitro fertilization surrogate gestational pregnancy programme. *Human Reproduction* **15**, 1075–1078.

Honig D Nave O, Adam R 2000 Israeli surrogacy law in practice. *Israel Journal of Psychiatry and Related Sciences* **37**, 115–123.

Marrs RP, Ringler GE, Vargyas JM *et al.* 1993 The use of surrogate gestational carriers for assisted reproductive technologies. *American Journal of Obstetrics and Gynecology* **168**, 1858–1863.

Meniru GI, Craft IL 1997 Experience with gestational surrogacy as a treatment for sterility resulting from hysterectomy. *Human Reproduction* **12**, 51–54.

Raziel A, Friedler S, Schachter M *et al.* 2000. Successful pregnancy after 24 consecutive fetal losses: lessons learned from surrogacy. *Fertility and Sterility* **74**, 104–106.

Serafini P, Tran C, Richardson A *et al.* 1994 In-vitro fertilization surrogacy. *Assisted Reproduction Reviews* **4**, 155–161.

Stafford-Bell MA, Copeland CM 2001 Surrogacy in Australia: implantation rates have implications for embryo quality and uterine receptivity. *Reproduction, Fertility and Development* **13**, 99–104.

Soderstrom-Anttila V, Blomqvist T, Foudila T *et al.* 2002 Experience of in-vitro fertilization surrogacy in Finland. *Acta Obstetricia et Gynecologica Scandinavica* **81**, 747–752.

Utian WH, Sheehan L, Goldfarb JM *et al.* 1985 Successful pregnancy after in-vitro fertilization–embryo transfer from an infertile woman to a surrogate. *New England Journal of Medicine* **313**, 1351–1352.

Van Steirteghem AC, Nagy Z, Joris H *et al.* 1993 High fertilization and implantation rates after intracytoplasmic sperm injection. *Human Reproduction* **8**, 1061–1066.

Wilkinson S 2003 The exploitation arguments against commercial surrogacy. *Bioethics* **17**, 169–187.

Woodward BJ, Norton WJ, Neuberg RW 2004 Case report: Grandma, mother and another – an intergenerational surrogacy using anonymous donated embryos. *Reproductive BioMedicine Online* **9**, 260–263.


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