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Outcome and follow-up of children born after IVF–surrogacy

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This study addresses various outcomes and follow-up of children born after IVF–surrogacy. Recent reports on perinatal outcome after IVF–surrogacy and on data generated by the Society of Assisted Reproductive Technology (SART) Registry between 1991 and 1995 were examined. A review of recently published perinatal outcomes of children born after IVF–surrogacy, including the developmental information of 110 children after the first 2 years of life, was undertaken. The birth weights for singleton pregnancies following IVF–surrogacy and IVF were similar, whereas the birth weights of twins and triplets born from the IVF–surrogates were significantly heavier than those delivered from conventional IVF patients. Preterm delivery was increased in twin and triplet gestations in all segments analysed. The incidence of low birth weight was significantly lower in children born after IVF surrogacy than in those born after IVF, for all births recorded. The incidence of congenital abnormalities following IVF and IVF–surrogacy was within the expected range for spontaneous conceptions. Speech delays were predominant in the multiple births, but neither speech nor motor delays persisted at 2 years of age in children born after IVF–surrogacy. These findings would imply that a gestational carrier would provide potential environmental benefits for the infant.

Key words: commissioning couples/developmental outcome/IVF–surrogacy/low birth weight/preterm birth

TABLE OF CONTENTS

Introduction
Collection of data
Comparison of IVF and IVF–surrogacy
Pregnancy outcome and child follow-up after IVF–surrogacy
Acknowledgements
References

Introduction

In-vitro fertilization-surrogacy (IVF–surrogacy) has been used as an assisted reproductive treatment (ART) alternative whereby a woman gestates genetically unrelated embryos produced in an IVF laboratory with the gametes of a commissioning couple. More infrequently, donated oocytes and eventually embryos are used as sources of gametes and concepti by the commissioning couple before transfer into the IVF–surrogate (Serafini *et al.*, 1998). The first pregnancy following IVF–surrogacy was reported approximately 15 years ago (Utian *et al.*, 1985), since when gestational surrogacy has become a viable remedy for couples who would otherwise be unable to produce a child because of a non-functional uterus, excessive medical risk associated with pregnancy, or from failed attempts at conception with standard treatment options (Sheean, 1989; Serhal, 1990; Feinman *et al.*, 1993; Serafini *et al.*, 1994; Meniru and Craft, 1997; Corson *et al.*, 1998; Batzofin *et al.*, 1999). The indications, medical and psychological screenings, and techniques have been comprehensively described in the ART literature (Serhal, 1990; Feinman *et al.*, 1993; Serafini *et al.*, 1994, 1999; Meniru and Craft, 1997; Ben-Rafael *et al.*, 1998; Corson *et al.*, 1998; Batzofin *et al.*, 1999).

The purpose of this review is to compare the evidence on perinatal outcome of children born after IVF–surrogacy gathered from the data generated by the American Society for Reproductive Medicine/Society for Assisted Reproductive Technology Registry between 1991 and 1995 (SART, 1993, 1994, 1995, 1996, 1998), along with another recently reported study (Parkinson *et al.*, 1999). In addition, the outcome of children born after IVF–surrogacy was compared with those born after conventional IVF, generated from the SART Registry and from several recent publications (Brinsden and Rizk, 1992; Rufat *et al.*, 1994; Bonduelle *et al.*, 1996; Kurinczuk and Bower, 1997; Olivennes *et al.*, 1997; Wolff *et al.*, 1997; Loft *et al.*, 1999; Montgomery *et al.*, 1999; Westergaard *et al.*, 1999). Reviewing the information on physical growth, and verbal and motor development during the first 2 years of life of children born after IVF–surrogacy (Parkinson *et al.*, 1998) fosters the current knowledge of this ART treatment.

Table I. Average length of gestation and infant birth weight in IVF–surrogates and IVF patients

	Singleton		Twin		Triplet	
	Surrogate	IVF	Surrogate	IVF	Surrogate	IVF
Gestation (weeks)	38.7 ± 0.3	38.7 ± 1.2	36.2 ± 0.4[a]	36.0 ± 0.2	35.5	33.5 ± 0.6
Birth weight (kg)	3.5 ± 0.07	3.1 ± 0.03	2.7 ± 0.06[a]	2.4 ± 0.04	2.7 ± 0.13[a]	1.9 ± 0.6

Values are mean ± SEM.
Surrogate = IVF–surrogates; IVF = IVF patients (Brinsden and Rizk, 1992).
[a]$P < 0.05$ compared with singleton births (modified from Parkinson *et al.*, 1999).

Collection of data

The original study has been detailed previously (Parkinson *et al.*, 1999). In brief, the survey comprised 95 IVF–surrogates who delivered 128 children conceived with oocytes provided either by infertile women ($n = 88$) or by oocyte donors (OD) ($n = 24$). The average age of the women was 37.7 ± 5.0 years (commissioning), 30.7 ± 4.5 years (OD), and 30.4 ± 4.7 years (IVF–surrogates). The data were collected by a detailed review of medical records from all patients who delivered live births, and by a questionnaire completed via telephone interviews with the obstetricians, paediatricians, IVF–surrogates, ovum donors, and the commissioning couples.

The neonatal variables examined included: birth weight, size for gestational age, congenital malformations, neonatal morbidity, and length of hospitalization in the intensive care unit. Preterm delivery (PTD) was defined as births occurring before 36 weeks gestation. Those infants weighing <10th percentile for their age were considered small for gestational age (SGA), and those >90th percentile were considered large for gestational age (LGA). Low birth weight (LBW) and very low birth weight (VLBW) were defined as the infant weighing <2500 and <1500 g respectively.

Additional findings on the developmental information in 110 children (63 singletons and 47 multiples) included physical growth, and verbal and motor development during the first and second years of life, as ascertained by the Gessell Revised Developmental Schedules (Parkinson *et al.*, 1998).

Results generated by the Society of Assisted Reproductive Technology (SART) in the US and Canada from 1991 to 1995 (SART, 1993, 1994, 1995) were surveyed, spanning the first report by the SART Registry to the last report available during the preparation of this manuscript. An evaluation of the data on conventional IVF and IVF–surrogacy was made, focusing primarily on the frequencies of births per embryo transfer procedure, single and multiple births, as well as the incidence of structural and functional malformations.

Statistical analysis

Data are represented as average ± SEM. Continuous variables were evaluated with Student's *t*-test, as well as linear regression and correlation. Statistical significance was based on the χ^2 and Fisher's exact tests for categorical data and comparison of proportions; an α level of 0.05 was considered statistically significant.

Comparison of IVF and IVF–surrogacy

In all, 65 singletons, 27 sets of twins and two sets of triplets, were analysed. Five multifetal pregnancies (three sets of quadruplets and two sets of triplets) were reduced to twins and were included in the analysis of twin gestations. There were neither stillbirths nor perinatal deaths.

As depicted in Table I, the gestational lengths for singleton pregnancies following IVF–surrogacy and conventional IVF were similar. However, IVF–surrogates carrying twin and triplet gestations delivered substantially earlier than those who gestated singleton pregnancies (36.2 ± 0.4 versus 35.5 versus 38.7 ± 0.3 weeks gestation respectively; $P < 0.001$). Infant weight paralleled gestational age, as demonstrated by a statistically significant correlation between both variables ($r = 0.7725$, power = 1, $P < 0.001$). Singleton infants born through IVF–surrogacy were significantly heavier than twins and triplets (3.5 ± 0.07 kg versus 2.7 ± 0.06 kg versus 2.7 ± 0.13 kg; $P < 0.001$). This trend was also evident by the infants born after IVF treatment (Brinsden and Risk, 1992; Rufat *et al.*, 1994; FIVNAT, 1997; Moise *et al.*, 1998; Westergaard *et al.*, 1999). The data also suggest that multiples born after IVF–surrogacy were considerably heavier than those born after conventional IVF treatment (2.7 ± 0.06 kg versus 2.4 ± 0.04 kg for twins, and 2.7 ± 0.13 versus 1.9 ± 0.6 kg for triplets; $P < 0.05$). Although there was a tendency for the birth of heavier singleton infants after IVF–surrogacy, there was a large weight distribution in both populations examined. The frequency of new-borns appropriate for gestational age (AGA) was greater in the offspring of IVF–surrogates who delivered twins and triplets (94.4 and 83.3%) as opposed to the singleton infants (67.2%; $P < 0.05$).

The vast majority of the IVF–surrogates who carried twins and triplets experienced preterm labour (46.3 and 100% respectively) and PTD (20.4 and 100% respectively) when compared with those who bore singleton gestations (11.5%) (Figure 1). Multiple infants carried by the IVF–surrogates were born between 30.5 and 36 weeks gestation (birth weight 1.7–3.8 kg), while the singleton new-borns were born between 28 to 41 weeks gestation (birth weight 1.25–4.8 kg).

The incidence of LBW was significantly lower in the children born after IVF surrogacy compared with those born after conventional IVF for all births recorded (singleton, twin and triplet) (Figure 2). In addition, there were no differences in the weight of twins and triplets delivered by the IVF–surrogates (29.6

versus 33.3% respectively). As anticipated, the frequency of LBW neonates was substantially greater in the multiple IVF–surrogacy gestations and conventional IVF than those recorded in the singleton pregnancies. While these findings mirror the data from IVF reported earlier (Brinsden and Rizk, 1992; FIVNAT, 1997; Moise *et al*., 1998; Westergaard *et al*., 1999), there was a significantly higher incidence (2- to 4-fold) of LBW in the singletons produced by IVF (Figure 2). In addition, a greater frequency (2-fold) of LBW twins and triplets (53 and 92%) was observed in the IVF patients as opposed to the IVF–surrogates (29.6 and 33.3%).

The incidence of multiple pregnancies following conventional IVF and IVF–surrogacy was 33.9% and 33.4% respectively. The majority of these pregnancies were twin gestations (27.3 and 28.6%).

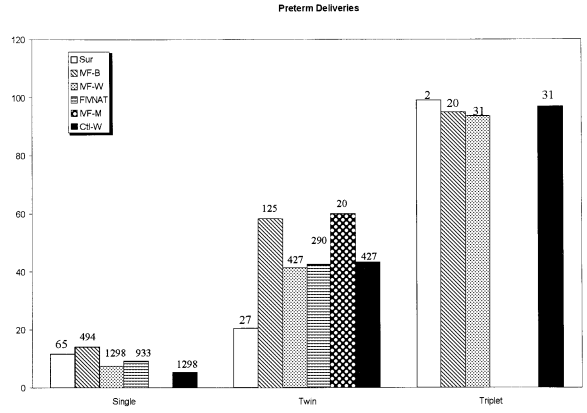

Figure 1. Comparison of percentages of preterm deliveries for singleton, twin and triplet births after IVF-surrogacy, IVF and controls. Sur = IVF–surrogate (Parkinson *et al.*, 1999); IVF-B = IVF patients (Brinsden and Rizk, 1992); IVF-W = IVF patients from Danish IVF registry (Westergaard *et al.*,1999); FIVNAT = IVF patients from French National Registry (FIVNAT, 1997); IVF-M = controlled study on twin pregnancies from Israel (Moise *et al*., 1998); Ctl-W = control data from the Danish Medical Birth Registry (Westergaard *et al.*,1999). Numbers above each bar indicate total numbers of patients.

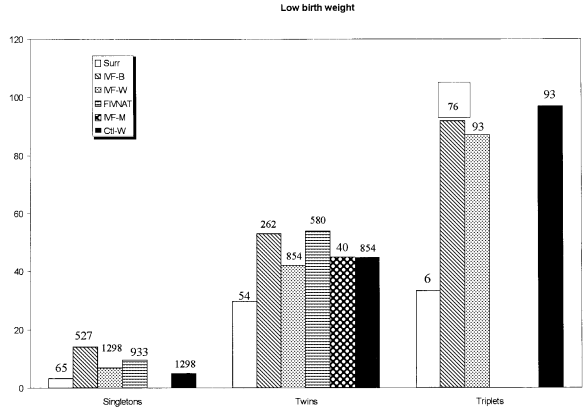

Figure 2. Comparison of percentages of low birth weight for singleton, twin, and triplet births after IVF–surrogacy, IVF and controls. Sur = IVF–surrogate (Parkinson *et al.*, 1999); IVF-B = IVF patients (Brinsden and Rizk, 1992); IVF-W = IVF patients from Danish IVF registry (Westergaard *et al.*,1999); FIVNAT = IVF patients from French National Registry (FIVNAT, 1997); IVF-M = controlled study on twin pregnancies from Israel (Moise *et al*., 1998); Ctl-W = control data from the Danish Medical Birth Registry (Westergaard *et al.*,1999). Numbers above each bar indicate total numbers of patients.

According to the results generated by the SART Registry, 281 clinics reported on the IVF outcomes, while 56 centres provided IVF–surrogacy assistance (SART, 1993, 1994, 1995, 1996, 1998). The total numbers of embryo transfer procedures following IVF and IVF–surrogacy in the 5 years surveyed were 117 425 and 863 respectively. The number of IVF and IVF–surrogacy deliveries, number of neonates, and the number of neonates with structural and functional malformations are shown in Table II. Birth rates after IVF and IVF–surrogacy were 26.8% (25 375) and 37.2% (265) respectively. The incidence of congenital abnormalities following conventional IVF and IVF–surrogacy was 1.82 and 2.92 per 100 births respectively, and the differences were not statistically significant (SART, 1993, 1994, 1995, 1996, 1998). The incidence of both minor and major congenital malformations in a previous study (Parkinson *et al.*, 1999) was in accord with the general population and the SART report.

Pregnancy outcome and child follow-up after IVF–surrogacy

The findings of this review raise various relevant facts of the current published scientific information on the outcome and follow-up of children born after IVF–surrogacy. A total of 265 deliveries for 863 embryo transfers performed in North America exceeds the meagre expectations conjectured in the literature. Unexpectedly, a large number of centres ($n = 56$) providing IVF–surrogacy assistance generated an apparently greater birth rate (37.2%) when compared with those rates after standard IVF (26.8%).

The observation of comparable gestational lengths for singleton pregnancies following IVF–surrogacy, IVF and non-reproductively assisted conceptions (Brinsden and Rizk, 1992; Rufat *et al*., 1994; Bonduelle *et al*., 1996; Olivennes *et al.*, 1997; Wolff *et al*., 1997; Corson *et al.*, 1998; Loft *et al*., 1999; Montgomery *et al.*, 1999; Parkinson *et al*., 1999; Westergaard *et al*., 1999) was reassuring. Furthermore, the statistically significant correlation between infant weight and gestational age added strength to the validity of the data following IVF–surrogacy. Although IVF–surrogates carrying twin and triplet gestations delivered substantially earlier than those who gestated singleton pregnancies, the overall lengths of pregnancy for singletons, twins and triplets in the IVF–surrogates and IVF patients were identical. The incidence of preterm delivery, one of the most challenging obstetrical problems and a leading cause of neonatal morbidity and mortality that complicates 8–12% of births in the US, varied from 5.3 to 14% in singleton pregnancies (Brinsden and Rizk, 1992; Lockwood, 1995; Singh and Yu, 1995; Westergaard *et al*., 1999). As previously acknowledged, prematurity following IVF has been predominantly caused by multiple pregnancy (Rufat *et al.*, 1994; Lockwood, 1995; Olivennes *et al*., 1997; Moise *et al*., 1998; Westergaard *et al*., 1999). An important discrepancy was identified regarding birth weight of infants delivered after IVF–surrogacy when compared with IVF patients. These findings reinforce potential benefits of a normal anatomy and the plasticity of the uterus generated by having previously delivered full-term pregnancies. The benefits of superior obstetrical care, along with the understanding of the commitment of a pregnancy (among

Table II. Annual numbers of births, neonates and combined structural and functional malformations for IVF and IVF–surrogacy[a]

Year	IVF births (*n*)	Surrogate births (*n*)	IVF neonates (*n*)	Surrogate neonates (*n*)	Malformations	
					IVF (*n*)	Surrogate (*n*)
1991	3215	35	3873	39	57	1
1992	4206	51	5689	58	109	4
1993	5103	78	6870	100	164	2
1994	4912	56	6339	70	174	2
1995	7939	45	11 259	65	83	0
Total	25 375	265	34 030	332	587 (1.7)	9 (2.7)

[a]Data obtained from clinics reporting to The American Society of Reproductive Medicine/Society for Assisted Reproductive Technology Registry between 1991 and 1995.

several other factors), might have positively contributed to the outcomes measured.

The significantly lower incidence of LBW observed in the children born after IVF surrogacy (as illustrated in Figure 2) and the lack of differences in the weight of twins and triplets delivered by the IVF–surrogates are consonant with the care provided by the gestational carriers.

The incidence of combined malformations (both minor and major) in the IVF–surrogates was comparable with IVF rates (Brinsden and Rizk, 1992; Westergaard *et al*., 1999); nevertheless, the sample size in this study was small and the interpretation of the data consequently limited. Clinically, congenital anomalies account for one in every five infant deaths, and are the leading cause of infant death in the US (Singh and Yu, 1995). Therefore, the comparable incidence of malformation in the children born after IVF–surrogacy to those of IVF patients, in addition to the absence of stillbirths and perinatal deaths, is very reassuring. However, all surveys should use the same definitions for the coding of malformations to decrease the inherent biases regarding the limits of definition.

The physical growth, and verbal and motor development of 110 children (63 singletons and 47 multiples) born after IVF–surrogacy showed a low incidence of slow physical growth for singletons (1.7%) and normal development for multiples (10%) when compared with spontaneously conceived children (up to 10%). Speech delays were predominant in the multiples (21.3 and 10.5% for the first and second years of life respectively). The incidence of speech delay for the singleton was 9.4 and 3.8%, for the first and second years respectively. There were no motor delays persisting at 2 years of age from single and multiple birth children after IVF–surrogacy. This information assumes great importance, since 17% of children in the US were reported to have had a developmental disability (Boyle *et al.*, 1994); this is equivalent to about one in every six children aged $\leqslant$17 years. Developmental disabilities are common health problems that can have major impact on a child's health and general ability to function.

Although many important questions have been answered through these basic studies on the outcome of children after IVF–surrogacy, many questions remain. Therefore, it is critical to raise awareness in the governmental and private agencies that conduct studies on all ART outcomes in order to obtain the greatest quantity of data that will provide the foundation for both preventive and early interventional medicine.

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