Journal of in Vitro Fertilization and Embryo Transfer, Vol. 3, No. 4, 1986

Developmental Assessment of Twenty in Vitro Fertilization (IVF) Infants at Their First Birthday

JOHN L. YOVICH,[1,2] TREVOR S. PARRY,[1,3] NOEL P. FRENCH,[1,3] and ALFRED A. GRAUAUG[1,4]

Submitted: October 7, 1985
Accepted: December 12, 1985 (Australian Editorial Office)

The pregnancy details, delivery outcome, and developmental status as measured on the Griffiths Developmental Scales are provided on the first 20 infants reaching their first birthday following in vitro fertilization–embryo transfer (IVF-ET) within the PIVET Programme. An increased rate of preterm delivery, intrauterine growth retardation, and cesarean sections was noted. One significant and two minor abnormalities were detected and only one infant was slightly under the expected developmental assessment at 1 year on the corrected general quotient of the Griffiths Developmental Scales for children.

KEY WORDS: in vitro fertilization; pregnancy outcome; neonatal assessment; pediatric developmental assessment.

See also Editorial comments on p. 258.

INTRODUCTION

In 1977, when embarking (JLY) on human in vitro fertilization and embryo transfer (IVF-ET) studies (1,2), it was uncertain whether normal human life could be generated by the technique. With the birth of Louise Brown in July 1978, it was reassuring that a comprehensive pediatric assessment excluded a recognizable congenital malformation (3) and the infant has subsequently developed normally (4). Accumulating information (5,6) indicates that IVF infants do develop normally and only isolated cases with congenital abnormalities have been reported (6,7).

The only unusual features noted from IVF pregnancies are the high rate of early pregnancy wastage and a higher than expected rate of preterm delivery (5). No information has yet appeared concerning definitive studies of developmental progress of IVF infants. This report deals with a comprehensive assessment of the first 20 IVF infants progressing past 20 weeks' gestation in the PIVET IVF Programme (8).

MATERIALS AND METHODS

An arrangement was undertaken with the Child Development Centre, Community Health Services Branch of the Health Department of Western Australia, for a full prospective developmental pediatric assessment on the first 20 infants delivered following IVF-ET. The first ongoing pregnancy was achieved during the pilot study at KEMH (9) and a healthy male infant was delivered in July 1982. The 19 further ongoing pregnancies were generated from the Service Programme (8) and all babies had reached their first birthday by February 22, 1985. All infants were examined at birth by two consultant pediatricians from the Department of Newborn Services, KEMH, and assessed during the neonatal period.

The developmental assessment at 1 year included a general pediatric history and examination noting the age of achievement of milestones, any unusual features, illnesses, weight gain, and general nutritional status. The Griffiths Developmental Scales for Children were applied for full developmental assessment (10,11) and the Stycar baby tests (12,13) were used to assess hearing and vision.

In all preterm babies the gestational age was as-

[1] University Department of Obstetrics and Gynaecology, King Edward Memorial Hospital, Subiaco, Perth, Western Australia.
[2] To whom correspondence should be addressed at PIVET Laboratory, 166-168 Cambridge Street, Leederville, Western Australia 6007.
[3] Child Development Centre, Community and Child Health Services, West Perth, Western Australia.
[4] Department of Newborn Services, King Edward Memorial Hospital, Subiaco, Perth, Western Australia.

0740-7769/86/0800-0253$05.00/0

sessed clinically using the Ballard *et al.* modification (14) of the Dubowitz assessment charts (15). The assessment of intrauterine growth retardation (IUGR) was determined from neonatal growth percentiles adapted from Naeye and Dixon (16) and which are known to be relevant to the local population.

Within the IVF program and as part of an ongoing study assessing the role of medroxyprogesterone acetate (MPA), patients who had bleeding in early pregnancy were given MPA, 20 mg, qid, beginning in the fifth to seventh week and continuing through to 18 weeks (17).

RESULTS

In Table I is given a summary of the pregnancy details and delivery outcome of the first 20 IVF infants arising from the PIVET IVF Programme. All the initial 20 pregnancies proceeding beyond 20 weeks eventuated in the delivery of live-born infants who have subsequently thrived. The mean gestational period at the time of delivery was 36.3 weeks. Six infants delivered preterm from four pregnancies (25% of pregnancies). Threatened abortion occurred in 11 pregnancies (69%) and MPA was given so that 14 infants (70%) were exposed to this drug during organogenesis and early intrauterine development.

Eight of the pregnancies (50%) were delivered by cesarean section, including the three multiple pregnancies. The scores in all infants were 7 or greater by 5 min. Six infants (five preterm) required some degree of respiratory assistance in the neonatal period. It can be seen that 16 of the 20 infants were male. One of the pairs of twins and possibly two of the triplet infants proved to be monozygotic.

Evidence of IUGR was noted in six infants including four preterm babies, one of which (of GT) was on the tenth percentile for gestational age (16) but had wasting and other clinical features characteristic of IUGR infants. The Ballard maturity rating scores corresponded with the estimated (from ET) clinical gestational age of all preterm infants including those small for gestational age. Fetal abnormalities were noted in three babies. One infant had the minor problem of bilateral hydrocoeles which resolved spontaneously. A second preterm infant had undescended testes and bilateral inguinal hernias which subsequently required surgery. The infant also suffered pyloric stenosis at 8 weeks, re-

Table I. PIVET IVF Programme: Pregnancy and Perinatal Data Relating to the First 20 IVF Infants

	Sex	Pregnancy complications[a]	Gestation at delivery (weeks)	Mode of delivery	Birth weight (g)	APGARS		Abnormalities	Neonatal complications[b]
						1 min	5 min		
1. LC	M	Th. ab. (MPA) IUGR	39	LUSCS	2340	9	9	IUGR	Nil
2. CG	F	PET	39	Vag	3285	8	9	Nil	Nil
3. NV	M	MZ twin	38	LUSCS	3050	9	9	Nil	Nil
4. NV	M	MZ twin	38	LUSCS	2680	9	9	Nil	Nil
5. KN	M	Th. ab. (MPA) breech	39	LUSCS	3380	7	9	Nil	Nil
6. DF	M	Th. ab. (MPA) breech	37	LUSCS	2200	8	8	IUGR	Isol
7. DF	F	Th. ab. (MPA)	37	LUSCS	3010	8	9	Nil	Nil
8. NT	M	Nil	38	Vag	2925	9	10	Nil	Nil
9. KT	F	Th. ab. (MPA)	39	Vag	3170	8	9	Nil	Nil
10. GP	M	Th. ab. (MPA)	40	Vag	3250	8	9	Nil	Nil
11. SW	M	Th. ab. (MPA) Pl.Pr	32	LUSCS	2020	3	9	Nil	R.A. (C)
12. FO	M	Th. ab. (MPA)	40	Vag	4550	9	9	Hydrocoeles	Nil
13. AA	M	Th. ab. (MPA) PROM	37	Vag	2540	9	9	Nil	R.A. (H)
14. JA	M	Th. ab. (MPA) IUGR	33	LUSCS	1475	2	9	IUGR[c]	R.A. (C)
15. RC	M	Th. ab. (MPA)	38	Vag	3310	9	9	Nil	Nil
16. GT	F	PET-IUGR	30	LUSCS	1330	3	7	IUGR	R.A. (C)
17. RA	M	Nil	39	Vag	3890	9	9	Nil	Nil
18. AW	M	Th. ab. (MPA)	31	LUSCS	1350	6	8	IUGR	R.A. (H)
19. AW	M	Th. ab. (MPA)	31	LUSCS	1355	7	8	IUGR	Isol
20. AW	M	Th. ab. (MPA)	31	LUSCS	1425	7	9	Goldenhar	R.A. (C)

[a] Th. ab., threatened abortion; PET, preeclamptic toxemia; MZ, monozygotic; Pl.Pr, placenta previa; PROM, premature rupture of membranes; IUGR, intrauterine growth retardation; LUSCS, cesarean section (lower segment).
[b] Isol, isolette; R.A., respiratory assistance; H, headbox oxygen; C, continuous positive airways pressure.
[c] This infant also had undescended testis, inguinal hernias, and pyloric stenosis.

Table II. Developmental Assessment at 1 Year of the First 20 IVF Infants

	General	Locomotion (months)	Personal/ social	Hearing & speech	Eye & Hand coordination	Per- formance	Chrono- logical age	Mental age		GQ		Corrected GQ
1. LC	Sleep problems	14	14	17.5	15.5	15.5	12.5	15.3		122		—
2. CG	Normal	13.5	14	14.5	13.5	14	12	13.9		116		—
3. NV	Normal	16.5	14.5	15	17.5	18	13	16.3		125		—
4. NV	Normal	16.5	14.5	14.5	17.5	16.5	13	15.9		122		—
5. KN	Sleep problems	16.5	14.5	14	15.5	14.5	12	15		125		—
6. DF	Normal	13	13	13.5	14	14	12.2	13.5		110		
7. DF	Normal	14.5	13	13.5	13.5	13.5	12.2	13.1		107		
8. NT	Normal	16	13	13.5	13.5	15	12.5	14.2		114		
9. KT	Normal	15	13.5	11.5	11.5	12.5	12	12.8		106.7		—
10. GP	Normal	15	15	13.5	16	15	12	14.9		124		—
11. SW	Normal	15	14.5	13	15.5	14	12	14.4		120		137
12. FO	Normal	19	18.5	19.5	18.5	19	13.25	18.9		143		—
13. AO	Normal	16	13.5	13.5	14	15	12	14.4		120		—
14. JA	Normal	10.5	10.5	9	11.5	10.5	12.5	10.4		83		95
15. RC	Normal	16	15	15.5	14.5	15.5	13.5	15.2		113		—
16. GT	Normal	12.5	13	14.5	14.5	13	12.5	13.5		108		129
17. RA	Normal	14	12.5	13	12.5	12	12.5	12.8		102		—
18. AW	Normal	14	11.5	14.5	11.5	11	13	12.5		96		113.6
19. AW	Normal	14	11.5	14.5	12	11	13	12.5		96.2		113.6
20. AW	Normal	14	11.5	14	11.5	10.5	13	12.3		94.6		111.8
								Total	Minus prems	Total	Minus prems	
	$\bar{X}$	14.78	13.55	14.1	14.2	14	12.53	14.09	14.72	107.02	117.83	117.48
	SD	±1.77	±1.69	±2.02	±2.09	±2.29	±0.47	±1.77	±1.57	±27.04	±10.03	±11.16

quiring surgical correction. The third infant had a deformed right pinna, two additional ribs, and two hemivertebrae, consistent with the syndrome described by Goldenhar (7).

The 1-year developmental assessments are summarized in Table II. All infants had progressed normally and the mothers reported no obvious concerns. The mean chronological age at which the infants were assessed was 12.53 months (SD, ±0.47) and it can be seen that the mean assessment for each scale of the Griffiths test was slightly in advance. The mean mental age was 14.09 ± 1.77 months, and if the preterm infants were excluded, this figure was 14.72 ± 1.57 months. The general quotient (GQ) for the 20 infants was 107.02 ± 27.04. If the preterm infants were excluded, this level increased to 117.8 ± 10. A corrected GQ was derived by deducting the months of prematurity from the chronological age of each of the preterm infants, giving an overall corrected GQ of 117.48 ± 11.16. Only one infant remained below 100 after correction. He was born at 33 weeks' gestation, with a birth weight of 1475 g. The low birth weight was considered to be due to a combination of preterm and IUGR features. He was the second infant with fetal abnormalities and had surgical treatments (described above). His progress in the Special Nursery was uncomplicated and he did not require respiratory assistance.

Generally a low level of parental anxiety was evident. Mothers did not appear to be apprehensively expecting abnormal developments related to their child's mode of conception and only two reported sleep problems among the infants. It may be of relevance that one of them was the first Western Australian mother of an IVF infant. She reported feeling somewhat vulnerably exposed because of news media interest, which persisted until other IVF infants were delivered several months later.

DISCUSSION

Of the first 20 infants delivered in the PIVET IVF-ET Programme, only one case of significant abnormality was noted and all but one other infant developed with a corrected GQ >100. The high cesarean section rate relates partly to the in-

creased proportion of multiple pregnancies in this group. Undoubtedly, it also reflects both patient and medical attendant apprehension regarding the risks of vaginal delivery when considered against the background of long-standing infertility and the high-cost, high-technology mode of conception. It is reassuring to note that those women who did deliver vaginally had normal infants who progressed well, implying that the decision regarding mode of delivery should rest strictly on obstetric features.

The findings of an increased risk of preterm delivery and possibly of IUGR is consistent with other reports (5) and the reasons relate to both multiple pregnancies and possibly the background history of infertility. A mechanism for the latter is not known or proposed but factors such as maternal age, apprehension, and possibly personality considerations should be taken into account.

The high proportion of males noted in the first 20 deliveries was not of statistical significance in view of the total number. Now that more than 50 infants have been delivered, the sex ratio has approached that normally expected, with only a slight increase in the male/female ratio. Collated data from numerous centers indicate no sex-ratio imbalance (5,6). The findings of monozygosity in a twin pair and possibly two of triplet infants has been presented and discussed previously (17,18). The phenomenon is unlikely to be related to IVF techniques. Fourteen babies were exposed to MPA and the implications concerning embryopathy have been discussed previously. Both the minor and the major cases of fetal anomaly were noted in MPA-treated infants but this was not a significant association. The only recurring association previously reported is that of glandular hypospadias (19,20).

Assessing urinary steroid profiles determined by gas–liquid chromatography and mass spectrometry adds further reassurance regarding MPA. Fourteen pregnant women treated during weeks 6 to 18 demonstrated no qualitative or quantitative alterations to the profile of steroid metabolites in urine (17).

It is reassuring to note that the developmental assessment for five test scales was in advance of the mean rates defined by Griffiths (10). However, it cannot be concluded that these infants have advanced development, as a control series was not defined or studied. Nevertheless, the concept of a general developmental quotient (GQ) has been standardized and continues to work surprisingly well in clinical practice (11). In this context it is fully reassuring to note that 19 of the 20 infants were above the corrected Griffiths GQ at their first birthday.

ACKNOWLEDGMENTS

The in vitro fertilization program was initiated by Grant 6-81/82 provided by the King Edward Memorial Hospital Research Foundation. Continued support has been provided by Grant 4L1RBZQ1083/84 from the University of Western Australia.

We particularly acknowledge Anne Tuvik, co-ordinating nurse for the PIVET IVF Programme, who has maintained the register for all pregnancies arising within the program.

REFERENCES

1. Craft I, Yovich JL: Implications of embryo transfer. Lancet 1979;2:642–643
2. Yovich J, Craft I: An independent extra-corporeal fertilization experience. Aust NZ J Obstet Gynaecol 1981;21:55
3. Hilson D, Bruce RL, Sims DG: Successful pregnancy following in-vitro fertilisation. Lancet 1978;2:473
4. Edwards RG: In-vitro fertilization and embryo replacement: Opening Lecture. In Proceedings of the III World Conference IVF-ET, Helsinki, May 14–17, 1984. Ann NY Acad Sci 1985;442:1–22
5. Lancaster PL: In-vitro fertilization pregnancies, Australia 1980–1983. National Perinatal Statistics Unit, 1984, Publication ISSN 0814-7205, Commonwealth Institute of Health, University of Sydney, N.S.W.
6. Seppälä M: The world collaborative report on in-vitro fertilization and embryo replacement: Current state of the art in January, 1984. In Proceedings of the III World Congress of In-vitro Fertilization and Embryo Transfer, Helsinki, Finland, May 1984. Ann NY Acad Sci 1985;442:558–563
7. Yovich JL, Stanger JD, Grauaug AA, Lunay GG, Hollingsworth P, Mulcahy M: Fetal abnormality (Goldenhar syndrome) occurring in one of triplet infants derived from in-vitro fertilization with possible monozygotic twinning. J Vitro Fert Embryo Transfer 1985;2:27–32
8. Yovich JL, Stanger JD, Tuvik AI, Yovich JM: In-vitro fertilization in Western Australia: A viable service programme. Med J Aust 1984;140:645–649
9. Yovich JL, Puzey A, De Atta R, Roberts R, Reid S, Grauaug A: In-vitro fertilisation pregnancy with early progestagen support. Lancet 1982;2:378–379
10. Griffiths R: The Abilities of Babies. A Study in Mental Measurement. London, University of London Press, 1954
11. Griffiths R: The Abilities of Babies. A Study in Mental Measurement. Norfolk, GB, Lowe and Brydone, 1976
12. Sheridan MD: Simple clinical hearing tests for very young and mentally retarded children. Br Med J 1958;2:999

13. Sheridan MD: Vision screening procedures for very young or handicapped children. Clin Dev Med 1969;32:39–47
14. Ballard J, Kazmaier K, Driver M: A simplified assessment of gestational age. Pediat Res 1977;11:374
15. Dubowitz LMS, Dubowitz V, Goldberg C: Clinical assessment of gestational age in the newborn infant. J Pediat 1970;77:1–10
16. Naeye RL, Dixon JB: Distortions in fetal growth standards. Pediat Res 1978;12:987–991
17. Yovich JL, Willcox DL, Wilkinson SP, Poletti VM, Hahnel R: Medroxyprogesterone acetate does not perturb the profile of steroid metabolites in urine during pregnancy. J Endocrinol 1985;104:453–459
18. Yovich JL, Stanger JD, Grauaug A, Barter RA, Lunay G, Dawkins R, Mulcahy MR: Monozygotic twins from in-vitro fertilization. Fertil Steril 1984;41:833–837
19. Burstein R, Wasserman HC: The effect of provera on the fetus. Obstet Gynecol 1964;23:931–934
20. Yovich JL, Stanger JD, Willcox DL, Michael CA: Medroxyprogesterone in in-vitro fertilisation. Lancet 1983;1:711