

Pregnancy outcome after *in vitro* fertilisation at the Pretoria unit

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Abstract This retrospective study was conducted to ascertain the success rate of a university-based *in vitro* fertilisation (IVF) programme. Over a 4-year period a total of 881 patients was aspirated with an 81,8% embryo transfer (ET) rate. This resulted in 150 biochemical pregnancies (20,8% per ET), and 92 births that produced 100 babies were recorded (12,8% per ET). Multiple pregnancies accounted for 8,7% of births and 6,5% of the 100 babies presented with minor congenital abnormalities. Delivery took place by caesarean section in 46% of cases. Birth mass of babies ranged from 1,06 to 4 kg with a mean of $2,944 \pm 0,629$ kg. Mean gestational age was $260 \pm 18,2$ days. Twenty-three percent of babies born were preterm, 13,8% of these were twins and presented with a low birth mass. It was concluded that the conception rate of patients did not differ with regard to the number of IVF attempts but that those who conceived during the first two attempts had a significantly better chance ($P < 0,05$) of carrying to term.

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In vitro fertilisation (IVF) and embryo transfer (ET) have established themselves as effective modalities in the treatment of sub-fertile patients.¹⁻³ The ultimate aim of IVF and ET is to attain optimum pregnancy rates and several factors should be considered in this endeavour. Factors influencing pregnancy rates have been documented previously³ and this investigation was undertaken to evaluate the outcome of patients who became pregnant after IVF and ET treatment at the Pretoria unit. Although numbers were a limiting factor, the incidence of repeated IVF attempts and their possible effect on pregnancy outcome were also considered. The incidence of biochemical pregnancy and the occurrence of fetal wastage thereafter, were evaluated against the number of ET attempts for each patient.

The following results were documented for the first 100 IVF babies born at the H. F. Verwoerd Hospital in Pretoria over a study period of 4 years and 4 months.

Subjects and methods

All patients who entered the IVF programme between October 1983 and February 1988 and subsequently became pregnant, were incorporated in this study (Table I). Since its inception, this unit has changed its IVF protocol substantially, thereby improving its effectiveness and raising the biochemical pregnancy rate from 12% to above 26% per ET. The stimulation protocol, laboratory protocol and other relevant procedures have already been documented.⁴

Biochemical pregnancies were considered positive if the serum levels of human chorionic gonadotrophin (HCG) were raised above 5 IU 10 days after ET. Analyses of HCG were performed by radio-immunoassay (DADE, Clinical Assay, Cambridge, Mass). After elevated HCG values were confirmed, pregnancies were followed up by ultrasonography as well as standard clinical investigations. Miscarriages occurring within 20 days

of ascertaining elevated HCG levels were defined as biochemical and those thereafter as clinical abortions. All ongoing pregnancies and births were recorded. Patients giving birth elsewhere were requested to telephone the clinic with the relevant information.

Statistics

The significance of probability was tested either with Yates's corrected χ^2 -test or Fisher's exact test.

Results

A total of 881 patients was aspirated by laparoscopic methods and 721 ETs (81,8%) were performed. These resulted in 150 biochemically defined pregnancies (20,8% per ET). A birth rate of 12,8% per ET was recorded. The number of patients treated consecutively was evenly distributed in terms of its being the first or second attempt (41,9% and 37,6%) but the number of attempts thereafter decreased significantly ($P < 0,01$; Table I).

Table II records the outcome of the 150 biochemical pregnancies and a total abortion rate of 36,7% for this study period was calculated. Ninety-two births were recorded including 8 sets of twins. There were thus 100 babies. The ratio of boys to girls was 0,89:1. If births per elevated HCG value are calculated, an increase in the abortion rate is detected from the third IVF attempt onwards. The combined abortion rate of attempts 1 and 2 is significantly lower ($P < 0,05$) when compared with the combined results of attempts 3 and 4. An overall

TABLE I.
Incidence of biochemical pregnancies and births as a percentage of all ET attempts

ET attempts	Total No. of ETs	Biochemical pregnancies		Births as % of total ETs
		No.	%	
1	302	63	20,9	14,6
2	271	45	16,6	11,1
3	93	20	21,5	10,8
4	36	14	38,9	11,1
5	11	4	36,4	18,2
6	8	4	50,0	25,0
Total	721	150	20,8	12,8

birth rate of 61,3% per elevated HCG was recorded (Table III). The number of embryos transferred plays a significant part in pregnancy outcome and transfer of 4 embryos contributed 35,3% to the total number of pregnancies documented. Pregnancies following transfer of 2 or 3 embryos did not perform as well as those following 4 embryos and contributed 25,3% and 22,7% respectively to the pregnancy pool. Multiple ETs had a remarkably better pregnancy rate compared with single ETs (16,7%) (Table IV).

Fig. 1 shows the age distribution of pregnant patients. The majority of pregnancies occurred within the 26 - 30-year (44,7%) and 31 - 35-year (37,3%) age groups. The under-25-year age group accounted for 6% and the over-35-year group for 18%. The abortion rate in all patients varied insignificantly from 33,3% to 44,4%.

TABLE II.
Distribution of biochemical pregnancies and births in consecutive ET attempts

ET attempts	No. of biochem. pregnancies	Biochem. abortions		Clinical abortions		Total abortions (%)	No. of ongoing pregnancies	No. of births	Babies		Total No. of babies	Births as % of HCG
		No.	%	No.	%				Boys	Girls		
1	63	6	9,5	12	19,1	28,6	1	44	19	28†	47	69,8
2	46	12	26,1	3	6,5	32,6	0	30	17	17†	34	66,7
3	19	2	10,5	7	36,8	47,3*	1	10	5	6	11	50,0*
4	14	4	28,6	6	42,9	71,4*	0	4	3	1	4	28,6*
5	4	1	25,0	1	25,0	50,0	0	2	1	1	2	50,0
6	4	0	0	1	25,0	25,0	1	2	2	0	2	50,0
Total	150	25	16,7	30	20,0	36,7	3	92	47	53	100	61,3

† Differ significantly from ($P < 0,05$).

TABLE III.
Distribution of biochemical pregnancies and births in relation to the number of embryos transferred

Embryos transferred	No. of patients with raised HCG	Births per No. of embryos transferred		Births as % of raised HCG
		No.	%	
1	25	11	11,96	44,0
2	38	23	25,0	60,5
3	34	24	26,1	70,6
4	53	34	36,96	64,2
Total	150	92		61,3

TABLE IV.
Relationship between ET attempts and number of embryos transferred

No. of embryos	ET attempt and resulting pregnancies						Total
	1	2	3	4	5	6	
1	11 (17,5%)	5 (11,1%)	6 (30,0%)	1 (7,1%)	1	1	25 (16,7%)
2	14 (22,2%)	13 (28,9%)	4 (20,0%)	6 (42,9%)		1	38 (25,3%)
3	12 (19,0%)	15 (33,3%)	4 (20,0%)	1 (7,1%)		2	34 (22,7%)
4	26 (41,3%)	12 (26,7%)	6 (30,0%)	6 (42,9%)	3		53 (35,3%)
Total	63	45	20	14	4	4	150

TABLE V.
Statistics on birth mass and gestational age (mean \pm SD)

	All babies	Male	Female
Mass at birth (kg)	2,944 \pm 0,629	3,018 \pm 0,566	2,874 \pm 0,612
Range (kg)	1,060 - 4,000	1,300 - 4,000	1,060 - 3,745
Low birth mass (\leq 2,5 kg)			
Singletons	3,085 \pm 0,817	(11,8% of births)	
Twins	2,408 \pm 0,389	(62,5% of births)	
Gestational age (days)			
Singletons	260 \pm 18,2	259 \pm 17,9	260 \pm 18,4
Twins	244 \pm 8,0		
% premature (\leq 252 days)			
Singletons	9,2		
Twins	13,8		
Total	23,0		

FIG. 1.

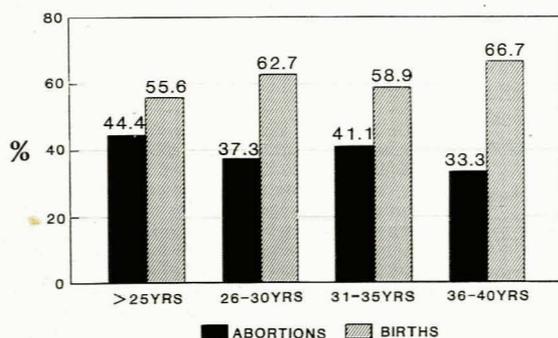


FIG. 1.
Distribution of patient age groups and pregnancy outcome in 150 biochemical pregnancies.

Caesarean sections accounted for 46% of births and 6,5% of babies born had congenital deformities. There were 2 babies with a cleft lip and palate, 1 with a minor atrial septum defect, and another with brain calcifications without apparent cause; 1 had a small cyst on the right labia minora. A major congenital malformation was encountered in a fetus born prematurely after 28 weeks' gestation. The karyotype was 46,XY. One still-birth was recorded caused by fetal cardiac failure after a car accident.

Birth mass averaged 2,944 \pm 0,629 kg (Table V) and ranged from 1,06 to 4 kg. Gestational age at birth averaged 260 \pm 16,4 days for singletons and 244 \pm 8 days ($P < 0,001$) for twins. Premature births were evident in 9,2% of singletons and 13,8% of twins thus accounting for 22,9% of all births. No difference existed between the sexes with regard to these parameters. Two mothers suffered from pre-eclampsia; one delivered vaginally at 31 weeks and the other had a caesarean section at 32 weeks.

Discussion

In this study of 721 ET attempts, 150 biochemical pregnancies resulted over a 4-year period with a mean pregnancy per ET rate of 20,8%. From the 150 preclinical pregnancies, a birth rate of 61,3% was documented. No obvious link could be observed between the pregnancy rate and successive IVF attempts. This is in accordance with the results published by Wood *et al.*² and Romeu *et al.*⁵ The latter, however, reported an insignificantly higher conception rate in patients treated for the first time. Although the number of previous treatments did not influence the pregnancy outcome in this study, it

was noted that there is a tendency towards increased pregnancy loss following successive IVF attempts (Table II). The combined data for attempts 1 and 2 versus attempts 3 and 4 reveal insignificantly different values for biochemical abortions (16,6% v. 17,4%). The clinical abortion rates for these combined attempts, however, differ remarkably (14,8% v. 36,3%). The overall abortion rates for transfers 1 and 2 were 28,5% and 35,6% respectively and differed significantly ($P < 0,05$) compared with 40,0% for cycle 3 and 71,4% for cycle 4. Because of insufficient numbers, no statistical validity could be ascribed to the abortion rates obtained in attempts 5 and 6 and they were consequently ignored.

Data obtained from collaborating IVF units, as reported by Medical Research International (MRI), indicated that the total abortion rate was 41,5% in 1985, 31,1% in 1986⁶ and 29% in 1988.⁷ Liu *et al.*⁸ reported an abortion rate of 37% in a study from the Jones Institute of which 4% were due to preclinical embryo wastage. Edmonds *et al.*,⁹ on the other hand, have reported a 57% occurrence of menstrual (biochemical) abortions, which is abnormally high if compared to the 19% abortion rate reported at the Helsinki meeting.¹⁰

Clinical abortion rates reported by Jones *et al.*¹¹ were 33% compared with 30% according to Cohen.¹⁰ These rates are very similar to the 29,9% rate published after the Helsinki congress.¹⁰

The overall biochemical (16,7%) and clinical (20,0%) abortion rates reported in this study fall well within the abovementioned limits. The abortion rate is marginally higher than that reported by the Norfolk group⁵ for the 25 - 39-year age group, but lower than the 33,3% pre-clinical and 26,6% clinical abortion rate for those 40 years and over. The MRI Registry for 1988 recorded an abortion rate of 60% in women over 40.⁷

The distribution of pregnancies in different age groups showed the highest concentration in those 26 - 35 years of age. No specific tendencies, however, could be ascertained from these observations and the abortion incidence varied between 33,3% and 44,4%. Results reported by the Norfolk group⁵ as well as the MRI report for 1988⁷ did not illustrate any significant differences in abortion rates in similar age groups. A previous report from our unit indicated a decrease in pregnancy rate with increased maternal age.⁴ This, however, was not substantiated in this study.

The effect of the number of embryos transferred on pregnancy outcome is well-documented.^{1,2,7} A total of 25 pregnancies was recorded after transfer of a single embryo, 16,7% of the total number of pregnancies (Table IV). Pregnancies recorded with the transfer of multiple embryos made up 25,3% (2 embryos), 22,7% (3 embryos) and 35,3% (4 embryos) respectively of the total number. After confirming a biochemical preg-

nancy, 44,0% of single embryo pregnancies resulted in births, compared with birth rates of 60,5%, 70,6% and 64,2% in cases where 2, 3 and 4 embryos were transferred. These substantial differences, however, could not be verified statistically.

It is clear from the above that patients may fall pregnant regardless of the number of embryos transferred or the number of IVF attempts. The birth rate is apparently enhanced when increased numbers of embryos are transferred, although limiting numbers again defies statistical validation. No prognostic value however could be obtained by microscopic scoring of embryo morphology and pregnancy outcome, as was suggested by Liu *et al.*⁸ and Puissant *et al.*¹²

Birth by caesarean section accounted for 46% of babies. The raised incidence of caesarean section is normal for patients treated for subfertility. The Helsinki report quoted caesarean sections in 49% of patients. The Australian register¹³ quoted 49% for singleton births; this figure rose to 100% for triplets. The high incidence of caesarean section probably reflects the obstetrician's concern as much as the obstetric need. Several factors such as frequent nulliparity, sterility and other variables associated with IVF, could further influence the method of delivery. Performing a caesarean section minimises the risk, and this rate will decline as IVF becomes more commonplace.

The incidence of congenital malformations was higher than the 2,1% mentioned in the Australian register¹³ as well as the 2,2% rate reported by the MRC working party¹⁴ on children conceived by IVF. The possibility of an increase in the incidence of chromosomal anomalies following treatment of patients with ovarian stimulants and ovulation induction,¹⁵ has not been confirmed. At least 10 000 births would be required to provide the necessary statistical power to detect deviations from the norm.¹⁴ Current available figures show a lower incidence of malformation in children born after IVF⁹ than in a normal population, but data to verify this are still incomplete.

The incidence of preterm delivery, (delivery at 36 weeks according to MRI definition)⁹ was significantly higher for twins ($P < 0,001$), with a 13,8% premature birth rate and an average gestational age of $244 \pm 8,0$ days. In the case of single pregnancies, 9,2% of babies were preterm with an average age of $260 \pm 16,4$ days. This is also reflected clearly in the low birth weight of twins; 62,5% were below 2,5 kg (mean mass = $2,408 \pm 0,389$ kg) compared to singletons, 11,8% of whom had a low birth weight and averaged $3,085 \pm 0,817$ kg. These observations are on a par with those of other reports^{7,13} on IVF. Other factors influencing birth weights such as smoking, alcohol consumption and other major stressful life events were not considered.¹⁵ Rothberg *et al.*¹⁵ have documented the influence of these factors on South African mothers and of interest is that the birth weights of IVF babies in this study are comparable to those of a typical high stress score group. This unqualified observation should, however, be considered against the fact that a large number of IVF babies were

delivered by caesarean section and were thus younger than children delivered vaginally at term.

IVF has done much to help infertile couples. The rate of conception presently achieved by most units is probably close to its maximum potential and is comparable to the conception rate of normal fertile couples (27 - 28%) under natural conditions.¹⁶ In order to improve the birth rate, the high rate of abortions encountered in patients needs to be investigated. The tendency toward increased abortion rates after repeated attempts could also point to a selection process for patients with inherent abnormalities; this would increase the abortion incidence. The relatively low birth weight of IVF babies could be a cause for concern but the lack of numbers defies statistical validation at this point.

This study reports on our findings with regard to babies born in an IVF programme. The eventual health and normality of children from this and similar programmes should be evaluated and reported in order to obtain a balanced view of the long-term successes of techniques in assisted reproduction.

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