

## OUTCOME OF PREGNANCY AFTER INFERTILITY

By

T. R. VARMA, R. H. PATEL AND R. K. BHATENA

### SUMMARY

Pregnancies following a period of infertility are considered to be at increased risk for fetus. During a period of 3 years from 1983 to 1985, 748 couples were seen in the infertility clinic and 515 women (68.9%) conceived. Fifteen patients moved out of the area, we analysed the outcome of pregnancies in the remaining 500 patients (Group 1) and compared with the outcome in the total obstetric population (Group 2) during the same period. The mean age at conception in the infertility group (Group 1) was 31.8 ( $\pm 2.7$ , 2SD) years as compared with 23.7 ( $\pm 2.9$ , 2SD) in the total hospital obstetric population (Group 2) ( $p < 0.05$ ). The incidence of spontaneous abortion in the two groups (8 and 6.2%) is not different ( $p > 0.05$ ). However, the incidence of ectopic pregnancy was higher (3.0%) in the Group 2 as compared with the incidence (1.5%) in Group 1 ( $p < 0.01$ ). The incidence of pre-existing hypertensive vascular disease (7.7%) complicating pregnancy and multiple pregnancy (4.1%) was significantly higher in the Group 1 as compared with the incidence (1.5% and 1.4% respectively) in the Group 2 ( $p < 0.01$ ). The incidence of induction of labour (29.5%) and elective operative deliveries (10.6%) was higher in the Group 1. ( $p < 0.01$ ). The incidence of infants with birth weight below the tenth centile (12.9%) the incidence of fetal distress in labour (14.6%) and low Apgar score (0.5) (9.5%) was higher in Group 1 but there was no difference in the Perinatal mortality rate between the two groups. In general babies and mothers do not seem to be at a disadvantage in the infertility group as compared with the outcome in the total obstetric group delivered our hospital, this may be because of the intensive antenatal care the patients receive in the infertility group.

### Introduction

Pregnancies following a period of infertility are considered to be at increased risk for fetus. There are reports of higher

incidence of spontaneous abortions, possibly associated with increased incidence of chromosomal abnormalities in women who seek treatment for subfertility (Boue and Boue, 1973; Illingworth, 1979). The drugs used to induce or to improve ovulation are incriminated with increased incidence of multiple pregnancy resulting in

*From: St. George's Hospital Medical School,  
Cranmer Terrace, London, SW17 0QT, U.K.*

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significant increase in perinatal morbidity and mortality; increased incidence of spontaneous abortion rate; and increased incidence of birth defects. (Adashi *et al*, 1979; Bishop, 1972; Garcia *et al*, 1977; Hack *et al*, 1972; Harlep, 1976). Conflicting reports of increase in the incidence of birth defects, which range between 2% to 12.7% neither substantiate nor refute the significance of the above observations (Bishop, 1972). Adashi *et al* (1979) stated that twinning constituted the single most important complications of drugs used for induction of ovulation which results in significant increase in perinatal mortality and morbidity. They did not consider there was an increase in the risk of abortions and in the incidence of birth defects which was only 3.1% and was not significantly different compared with commonly quoted rates for the population at large. Clomiphene has been associated with congenital abnormalities, commonly the neural-tube defect (Barrett and Hakim, 1973; Dyson and Kohler, 1973; Field and Kerr, 1974; Sandler, 1973) and multiple non-specific fetal anomalies (Berman, 1975; Ylikorkala, 1975). After tubal surgery, either microscopic or macroscopic, the ectopic pregnancy rate is about 10% (Siegler, 1977).

#### Patients and Methods

During a period of 3 years from 1983 to 1985, 748 couples were seen in the infertility clinic and 515 women (68.9%) conceived. Fifteen patients moved out of the area after confirming their pregnancy using ultrasonic examination and follow-up of the outcome was not possible. Records of all patients who conceived were maintained until the final outcome of the pregnancy was known. Pregnancy was confirmed in all patients using ultrasonic examination. All the patients who

continued with the pregnancies chose to be delivered at St. George's Hospital hence data collection was accurate and easy.

The outcome of the 500 patients who conceived following their visit to the fertility clinic was compared to the outcome of the total obstetric population who visited the antenatal clinic at St. George's Hospital. Pregnancy was confirmed in all patients using ultrasonic examination following their visit to the antenatal clinic. Duration of pregnancy was known in all pregnancies since it was routine practice to use ultrasonic examination to assess gestational age for all patients booked to have their babies at St. George's Hospital.

We decided to compare the outcome of pregnancy in the two groups to evaluate pregnancies following previous infertility which was thought to be at increased risk of fetal problems.

#### Results

The mean age at conception was 31.8 ( $\pm 2.7$ , 2SD) years in the infertility group (Group 1) as compared with 23.7 ( $\pm 2.9$ , 2SD) years in the total hospital obstetric population (Group 2). The difference was significant ( $P < 0.05$ ). Fifty-one per cent were primigravidae in the infertility group as compared with 45.4 per cent in the total obstetric population group. The difference was not significant ( $P > 0.05$ ).

Table I shows the age distribution in the two Groups 1 and 2.

Table I shows that 43.4 per cent of women in group 1 were aged more than 30 years as compared with 25.6 per cent in Group 2, the difference was significant ( $P < 0.05$ ).

Table II shows the incidence of spontaneous abortions and ectopic pregnancy in the two groups.

TABLE I  
Age Distribution in the Infertility Two Groups

AGE (years)	GROUP 1 (Total No. 500)		GROUP 2 (Total No. 7893)	
	No.	(%)	No.	(%)
≤ 20	—	—	1046	(13.3)
21-25	70	(14.0)	2296	(29.1)
26-30	213	(42.6)	2489	(31.5)
31-35	159	(31.8)	1471	(18.6)
≥ 36	58	(11.6)	591	(7.5)
Total:	500	(100.0)	7893	(100.0)

TABLE II  
Incidence of Abortions and Ectopic Gestation in the Two Groups

	GROUP 1		GROUP 2	
	No.	(%)	No.	(%)
Abortion	41	( 8.0)	491	( 6.2)
Ectopic pregnancy	15	( 3.0)	118	( 1.5)
Remaining patients with ongoing pregnancy	444	(89.0)	7284	(92.3)
Total:	500	(100)	7893	(100)

The difference between the incidence of spontaneous abortion in the two groups 1 and 2 respectively were 8 and 6.2 per cent and the difference is not significant ( $P > 0.05$ ). One of the patients in Group 1 aborted an anencephalic fetus following prostaglandin termination at 16 weeks gestation following ultrasonic examination at 14 weeks gestation. However, the incidence of ectopic pregnancy is significantly higher in the Group 1 (3.0%) as compared with 1.5 per cent in Group 2, the difference is significant ( $P < 0.01$ ).

Table III shows the incidence of major complications in the remaining patients (444) in Group 1 and (7284) in Group 2.

Pre-existing hypertensive vascular disease complicating pregnancy was more common in Group 1 (7.7%) as compared with the incidence in Group 2 (1.5%). The reason for this may be due to increas-

ed incidence of women aged 36 or more years in Group 1. The incidence of multiple pregnancy was 4.1 per cent in Group 1 as compared with the incidence of 1.4 per cent in Group 2. ( $P < 0.05$ ). The incidence of premature labour and premature rupture of membranes in Group 1 is significantly lower (5.4% and 1.4% respectively) as compared with the incidence in Group 2 (10.8% and 3.0% respectively). The patients in Group 1 received probably close antenatal care and monitoring and also prophylactic ritodrine hydrochloride in all at risk patients, may be the reason for the significantly lower incidence of premature labour. None of the patients in Group 1 had clinical diabetes, whereas 0.3 per cent in the Group 2 had pre-existing diabetes. However 2 per cent of patients in Group 1 had gestational diabetes as compared with 0.9 per cent in Group 2 ( $P < 0.05$ ).

TABLE III  
Incidence of Major Complications in the Two Groups

Complications	GROUP 1 Total No. 444)		GROUP 2 (Total No. 7284)	
	No.	(%)	No.	(%)
Hypertensive vascular disease	34	(7.7)	113	(1.5)
Pregnancy related hypertension	54	(12.2)	914	(12.5)
Bleeding in early (pregnancy < 26 weeks)	19	(4.3)	269	(3.7)
Placenta praevia	9	(2.0)	78	(1.1)
Abruptio placentae	4	(0.9)	92	(1.3)
Diabetes	—	—	20	(0.3)
Gestational diabetes	9	(2.0)	67	(0.9)
Multiple pregnancy	18	(4.1)	100	(1.4)
Premature labour (< 37 weeks)	24	(5.4)	394	(5.4)
Premature rupture of membranes (< 37 weeks)	6	(1.4)	218	(3.0)
Cervical cerclage	12	(2.7)	159	(2.2)

Table IV shows the incidence of induction of labour and mode of delivery in Groups 1 and 2.

The incidence of induction of labour in Group 1 is significantly higher in Group 1 (29.5%) as compared with 17.3 per cent in Group 2. The reason for this may be due to increase in the number of older women and increased incidence of pre-existing hypertensive vascular disease in Group 1. The incidence of elective caesarean section is also higher in Group 1 (10.6% as compared with 5.0 per cent in

Group 2 ( $P < 0.05$ ) probably for the same reason such as higher number of older women, increased incidence of pre-existing hypertension, increased incidence of gestational diabetes, multiple pregnancy and history of previous long period of infertility. The incidence of forceps delivery and emergency caesarean section in labour does not appear to be different for the two groups. The incidence of fetal distress is higher in Group 1 (14.6%) as compared with the incidence in Group 2 (11.0%) and it may be due to an increas-

TABLE IV  
Incidence of Induction of Labour and Mode of Delivery in the Two Groups

Characteristics of labour and delivery	GROUP 1 (Total No. 444)		GROUP 2 (Total No. 7284)	
	No.	(%)	No.	(%)
Spontaneous labour	266	(59.9)	5654	(77.7)
Induced	131	(29.5)	1260	(17.3)
Elective Caesarean section	47	(10.6)	370	(5.0)
Normal vaginal delivery	275	(61.9)	5192	(71.3)
Forceps delivery	69	(15.5)	872	(12.0)
Ventouse	11	(2.5)	218	(3.0)
Emergency Caesarean section	42	(9.5)	632	(8.7)
Fetal distress in labour	65	(14.6)	804	(11.0)

ed incidence of growth retarded infants in Group 1.

Table V shows the duration of gestation at delivery in the Groups 1 and 2.

The incidence of delivery before 37 weeks in Group 1 was 6.8 per cent compared with 10.0 per cent in Group 2. The difference is significant ( $P < 0.01$ ). However, 10.9 per cent of patients delivered after 41 weeks gestation in Group 2 as compared with 6.1 per cent in the Group 1 ( $P < 0.01$ ). Reduced incidence of pre-term labour in Group 1 may be due to intense antenatal care and monitoring of

patients in Group 1 and the reduced incidence of delivery after 41 weeks is due to intervention by obstetrician for maternal and fetal reasons.

Table VI shows the birth weight of infants in the Groups 1 and 2.

In Group 1, 12.5 per cent of infants weighed less than 2500 gms as compared with 11.5 per cent in Group 2. The difference is not significant. There is no difference in the incidence of infants weighing 4000 or more gms in the two groups.

Table VII shows the condition of infants at birth in the Groups 1 and 2.

TABLE V  
*Duration of Gestation at Delivery in the Two Groups*

Duration of gestation (weeks)	GROUP 1 (Total No. 444)		GROUP 2 (Total No. 7284)	
	No.	(%)	No.	(%)
< 28	4	(0.9)	88	(1.2)
28-32	6	(1.4)	250	(3.4)
33-36	20	(4.5)	394	(5.4)
37-41	387	(87.1)	5751	(79.1)
> 41	27	(6.1)	801	(10.9)
Total:	444	(100.0)	7284	(100.0)

TABLE VI  
*The Birth Weight of Infants in the Two Groups*

Birth weight of infants (Gms.)	GROUP 1 (Total No. 464)		GROUP 2 (Total No. 7384)	
	No.	(%)	No.	(%)
< 1000	5	(1.1)	92	(1.2)
1000-1499	5	(1.1)	141	(1.9)
1500-1999	3	(0.6)	191	(2.6)
2000-2499	45	(9.7)	427	(5.8)
2500-2999	116	(25.0)	1451	(19.7)
3000-3499	262	(56.5)	4585	(62.1)
4000	28	(6.0)	497	(6.7)
Total:	464	(100.0)	7384	(100.0)

TABLE VII  
Condition of Infants at Birth in the Two Groups

Characteristics of infants at birth	GROUP 1 (Total No. 464)		GROUP 2 (Total No. 7384)	
	No.	(%)	No.	(%)
<i>SEX</i>				
Female	230	(49.5)	3544	(48.0)
Male	234	(50.5)	3840	(52.0)
<i>WEIGHT</i>				
< 2500 gm	58	(12.5)	851	(11.5)
< 10th percentile	60	(12.9)	634	(8.6)
<i>APGAR SCORE</i>				
0-5	44	(9.5)	396	(5.4)
P.N.M.R.	5	(10.8/1000)	75	(10.2/1000)
<i>STILL BIRTH</i>	4	(8.6/1000)	41	(5.6/1000)
N.N.D.	1	(2.2/1000)	34	(4.6/1000)
<i>FETAL ANOMALIES</i>				
Major	2	(0.4)	21	(0.3)
Minor	3	(0.6)	104	(1.4)

There is no difference in the sex distribution in the two groups. The incidence of infants with birth weight below the 10th centile was higher in the Group 1 (12.9%) as compared with the incidence in the Group 2 (8.6%) ( $P < 0.05$ ). The rate of low apgar score (0-5) was significantly higher in the Group 1 (9.5%) as compared with the rate in the Group 2 (5.4%) ( $P < 0.01$ ). This may be due to increased incidence of intrauterine growth retardation and increased incidence of operative intervention in women with pre-existing hypertension. There is no difference in the PNMR in the two groups though the still birth was higher in the Group 1 and the neo-natal death rate was higher in the Group 2. There was no difference in the incidence of fetal anomalies in the two groups. There were 4 still births in the Group 1. One patient was 30 years old with previous history of 4 first trimester abortions, subsequently received clomiphene for secondary infertility. Fetus developed hydrocephalus at 31 weeks and died in-utero, labour was in-

duced, a male infant weighing 1,200 gms with multiple malformation was born at 31 weeks gestation. Two babies were born following intrauterine death at 37 weeks. Both babies were significantly growth retarded, one following tubal surgery and the other following induction of ovulation using clomiphene. The fourth one was still-born at 32 weeks following intrauterine growth retardation and abruptio-placentae. The only one neo-natal death was associated with male infant born at 25 weeks gestation weighing 750 gms to a mother aged 36 years who received treatment using HMG and HCG for prolonged secondary amenorrhoea. One baby was born with gross fetal anomalies following clomiphene therapy and another one had spinabifida following clomiphene therapy for secondary infertility and was terminated at 16 weeks gestation which is included in the abortion group. Three infants had minor abnormalities such as extra digits.

All the statistical analysis within the

study was performed using Chi-square and students *t* test.

### Discussion

This study was prospective and based on patients who were seen in one hospital during a period of 3 years from 1983 to 1985 inclusive. Pregnancies following a period of infertility was thought to be at increased risk for fetus. Dyson and Kohler (1973) and James (1973) felt that the underlying subfertility might have a more important role in the increased incidence of neural tube defect, in the group of women who had ovulation induction. Ahlgren *et al* (1976) reported that 141 of 159 pregnancies conceived after clomiphene therapy ended in childbirth, including 7 sets of twins. They stated that there was an increase in the number of infants born with major malformation, which were exclusively to women who had not previously borne a normal infant. The incidence compared well with that published after gonadotrophin therapy. They suggested that the possibly higher incidence of malformations seen after drug induced ovulation would therefore seem to be due to the underlying subfertility state and thus not a direct drug effect. We had 2 patients who received clomiphene for secondary infertility. Both had 4 first trimester abortions in the past and both delivered infants with major malformations, one had spina bifida and the other had hydrocephalus and other anomalies. Boue and Boue (1973) reported an increased frequency of chromosomal anomalies in abortion after induced ovulation. He studied 1457 spontaneous abortions in the first trimester of the pregnancy and showed 892 (61%) had abnormal karyotype, more commonly occurred during the treatment cycle and if pregnancy occurred

immediately after the treatment cycle. The two patients in our study who had malformed fetus, conceived during clomiphene therapy. Of the 500 patients who attended the clinic 347 patients received clomiphene either alone or in combination with other medications and only 2 had fetal problems. In series on clomiphene conceptions, congenital abnormality rates vary between 2.1 to 5.4 per cent. (Hack *et al* 1972; Ahlgren *et al* 1976; Adashi *et al*, 1979) partly due to different definitions. The general impression is that, if there is any increase, it is slight and no specific abnormality is identified. Forty-three patients received gonadotrophins on its own or in combination with other drugs and thirtysix patients received Bromocriptine alone or in combination with other drugs and none had any problems of fetal anomaly. Bromocriptine was not associated with any congenital abnormalities despite it being taken after conception, which agrees with previous reports (Griffith *et al*, 1978).

We found no increase in the incidence of spontaneous abortion in the infertility group compared with the incidence in the total obstetric population group. Maresh and Chamberlain (1982) reported that the incidence of spontaneous abortion in the group they studied was 9 per cent. They followed up 136 pregnant women with a history of previous infertility, one patient had ectopic pregnancy, one had therapeutic abortion for fetal abnormality and 123 viable pregnancies. Fiftyeight per cent went into spontaneous labour as compared with 59.7 per cent in our study. Nearly 12 per cent in their study delivered before 37 weeks compared with 6.8 per cent in our study.

In general, patients with previous infertility do not seem to be at a greater

disadvantage as compared with the outcome in the total obstetric population booked to have their babies in our department, probably might be due to the intensive and close antenatal and intranatal care the patients receive in the Group 1, because of the higher incidence of older women, pre-existing hypertension, intra-uterine growth retardation and multiple pregnancy.

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