INFERTILITY—AETIOLOGY UNEXPLAINED

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'Review of the case records of 2086 consecutive couples registered for infertility evaluation over a period of 7 years revealed A group of patients whose infertility remained unexplained after completion of a standard protocol of investigations'. The incidence of this condition in this population was 23.58%. All these patients had infertility of at least 1 year's duration. In this 'Unexplained Infertility' group, 35.77% achieved spontaneous conception in 1 month to 1 year 10 months. The conception rate was unaltered by age of the female upto 30 years (around 40%) and declined sharply beyond that. Pregnancy rate showed a definite decrease with incresing duration of infertility, from 49% at 1 year and 45% at 2 years to 30% and below at 5 years and beyond.

Of the 176 women who became pregnant, 75.56% did so within 6 months of investigation and 97.15% within 1 year. However, in young women upto 25 years, 31.50% of the conceptions occurred after 6 Months of registration. Around 25% of the pregnancies conceived by women with 1 to 5 years of infertility were recorded after 6 months of registeration. Only around 9% of the total conceptions were recorded in women past the age of 30.

In view of these observations it is held that in women with no explainable cause for infertility, if she is young (30 years or less) and having short period of infertility (5 years or less), optimistic waiting for a period of 6 months to 1 year is justifiable, and it is preferable that the invasive and expensive investigative procedures are defferred, to give reasonable time for spontaneous conception to result.

We also feel that the various empirical therapeutic modalities employed, such as regulation of ovulation with clomiphene citrate, do not significantly improve the pregnancy rate in women with 'Unexplained infertility'. Results are poor for 'Fertility Laparotomy'.

Of the 40 subjects who failed to conceive, when further investigated, revealed a pelvic factor responsible for infertility following laparoscopy/laparotomy in 9 (22.50%), endocrine dysfunction in 2 (5.00%), explanation for infertility detected in 27.50% signifies the role of comprehensive investigation in intractable subjects. Thus it is evident that elaborate evaluation is mandatory in those infertile women with 'No Cause Detected' if (i) they fail to conceive within a reasonable

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period, (ii) above 30 years, or (iii) married for more than 5 years.

Introduction

Clinicians are becoming increasingly aware of a significant proportion of patients attending the infertility clinic whose infertility remains 'unexplained' or 'idiopathic', after completion of all the conventional diagnostic tests (Sher and Katz, 1976; Lenton *et al* 1977; Rajan *et al* 1980; Wallach, 1980; Thomas and Forest, 1980; and Templeton and Penney, 1982). The incidence of unexplained infertility remains unknown, and a review of clinic based studies reveals incidences ranging from 6 to 60% (Smith and Horger, 1967; Southam, 1960; and Thomas and Forrest, 1980). These differences in incidence may be attributed to referral patterns, investigation protocols and definitions of normal fertility. Available investigative procedures at a particular centre will certainly influence the incidence of unexplained infertility, because the use of laparoscopy as against HSG for diagnosis of tubal function and RIA study of hormone profile have reduced the incidence of this condition (Drake *et al* 1977).

An interesting and pleasant observation in the 'no-cause-detected' patients is the occurrence of spontaneous conception in a good number of them without any form of recognised treatment (Lenton, *et al* 1977; Rajan and Joseph, 1979; and Templeton, and Penney, 1982). This observation is instrumental for the advice of optimistic waiting practised in patients with no definite abnormality detected by the available investigations. Some authors (Sher and Katz, 1976; Thomas and Forrest, 1980, and Rajan and Devi, 1982) have tried to improve the pregnancy rate by certain forms of empirical treatment, such as cervical cauterisation, antibiotic therapy, ovulation regulation with clomiphene citrate, bromocriptine or gonadotropins, and by performing fertility-laparotomy'.

Since August, 1975, we were investigating infertile couples on a standard protocol which included (i) history and examination of both partners, (ii) Semen analysis, (iii), Post-coital test, (iv) premenstrual endometrial biopsy, (v) Basal body temperature recording wherever possible, and (vi) Evaluation of tubal patency by air insufflation method initially during the first year, but subsequently with Hysterosalpingography (HSG) as a regular investigation in all patients. If these conventional tests failed to demonstrate any abnormalities a diagnosis of "unexplained" or "idiopathic" infertility was made. These patients were advise vaginal antibiotics, in some subjects cauterisation of cervix, and placebo therapy with some vitamins. They were also advised on the proper coital frequency. Only if conception did not occur in a reasonable period they were scheduled for detailed investigations, which included laparoscopy and endocrine evaluation.

A group of unexplained infertility patients were administered clomiphene citrate for regulation of ovulation (Rajan and Devi, 1980), and this treatment was aimed at improving the pregnancy rate over that of conservative waiting. Recently we are treating a small group of such patients with bromocriptine. Fertility laparotomy, which included transfundal chromotubation, wedge resection of ovaries and ventral suspension of the uterus by the Baldy-Webster technic, was attempted in a small group of patients. These laparotomies were performed essentially as a diagnostic measure in unexplained infertility of long duration. However, presently we prefer a regular laparoscopic examination of all patients who fail to conceive or those with

long duration of infertility and probably elderly.

This presentation deals with our experience with unexplained infertility gained over a period of 7 years. Incidence of unexplained infertility in our service, percentage of spontaneous conception in them, influence of age and duration of infertility on the conception rate, advisability of hopeful waiting after the conventional diagnostic procedures, role of clomiphene therapy and fertility laparotomy in further improving the conception rate, and evaluation of the incidence of organic pathology in the 'unexplained' group following comprehensive laparoscopic and endocrine studies, are the different aspects considered in this study.

Materials and Methods

Beginning from August 1975, over a period of 7 years 2086 couples were registered for investigation and treatment of infertility. As per our investigative protocol (mentioned earlier) 492 were considered to have no explainable cause for infertility. This gives an incidence of 23.58%. Age of the female partners with unexplained infertility ranged from 17 to 39 years, with a mean of 27.42 years, and 96 (19.50%) were above 30 years. Their duration of infertility had ranged from 1 to 26 years with a mean of 5.38 years, and 127 (25.81%) were married for more than 5 years. Period of follow-up from the date of registration ranged from 1 month to 26 months, with a mean of 5.36 months, and 123 (25.00%) had been followed for more than 6 months.

In a group of 132 patients, ovulation regulation with clomiphene citrate (50 mg for 5 days from the 5th day of the cycle) was tried for 3 to 6 cycles. Similarly bromocriptine was tried in 12 subjects in the form of cyclical therapy, in a dose of 2.5 mg per day for 20 to 22 days from the 5th day of the cycle. Another form of empirical therapy attempted in this series was 'fertility laparotomy' performed in 12 subjects.

Observations

Considering all the couples registered, including those who did not have regular follow-up, among the 492 couples who were diagnosed to have 'unexplained infertility' 176 achieved a conception, a conception rate of 35.77%. These pregnancies have occurred within 1 to 22 months of initial registeration, the mean period of follow-up interval for conception being 4.60 months. Seventyfive per cent of the pregnancies (133 of 176 pregnancies) have been recorded within 6 months and 97% (171 pregnancies) within 1 year of registeration (Table I).

Age of the female partner had significantly influenced the conception rate. In the two lower age groups of upto 25 years and between 26 and 30 years the pregnancy rate had remained the same, 40.35% and 40.47% respectively. However, the pregnancy rate was very low between 31

TABLE I

Cumulative Conception in Spontaneous Pregnancies

(TOTAL PREGNANCIES: 176)

Pregnancies	1 to 3 months	4 to 6 months	7 to 9 months	10 to 12 months	Above 1 year	Above 2 years
Total pregnancies	91	133	159	171	176	nil
Percentage	51.70	75.56	90.34	97.16	100.00	—

and 35 years (18.46%), and above 35 years (12.90%), (Table II). Moreover, of the 176 pregnancies, only 16 (9.09%) were conceived in women above the age of 30 years.

Another factor influencing the rate of spontaneous conception was the duration of infertility. Rate of conception showed a definite decline with increasing duration of infertility. Conception rate was as high as 49% in those with 1 year infertility, which declined to 45.60% for 2 years and 40% for 3 years. Between 4 and 5 years the pregnancy rate had ranged from 35 to 30%. But beyond 5 years the rate was below 20% (Table III).

Considering the age of the female partner and period of follow-up after the investigations, the following observations were made: Among the 92 pregnancies recorded in women upto 25 years of age, 29 (31.52%) pregnancies have occurred after 6 months of waiting. Whereas number of pregnancies conceived after 6 months of waiting was as low as 17% and 12% after 25 years of age (Table IV).

TABLE II

Relation of Age and Pregnancy Rate in 'Unexplained Infertility'

Age group	Total patients with no factor	Total patients conceived spontaneously	Percentage
17 to 25 years	228	92	40.35
26 to 30 years	168	68	40.47
31 to 35 years	65	12	18.46
36 to 39 years	31	4	12.90
Total:	492	176	35.77

TABLE III

Duration of Infertility and Pregnancy Rate

Particulars	1 year	2 years	3 years	4 years	5 years	6 to 10	above 10
Total Patients	51	127	91	58	39	93	33
Total pregnant	25	60	37	21	12	18	3
Pregnancy (%)	49.02	45.60	40.00	35.09	30.77	19.57	9.09

TABLE IV

Relation of Age and Period of Follow-up in 176 Pregnancies

Age of patient	Registeration to pregnancy interval					
	1 to 6 months		7 to 12 months		more than 1 year	
	No. preg.	%age	No. preg.	%age	No. preg.	%age
17 to 25 years	63	68.48	24	26.09	5	5.43
26 to 30 years	56	82.35	12	17.65	nil	
31 to 39 years	14	87.50	2	12.50	nil	

However, such a comparison between duration of infertility and period of follow-up revealed that irrespective of duration of infertility, about 25% of the total pregnancies have been conceived after 6 months of waiting, (Table V).

Analysis of the pregnancy rate in 127 women who were treated with clomiphene citrate revealed a conception rate of 35.43%, with 45 subjects conceiving during the cycle of therapy. Nontheless, of the 365 women who were not treated with clomiphene 131 became pregnant spontaneously (35.89%) (Table VI). Among the 12 subjects in whom no pelvic pathology was detected at the time of fertility-laparotomy, 2 patients became pregnant post-operatively (16.66%). Another 12 subjects who had failed to conceive spontaneously or with any form of empirical therapy were started on bromocriptine therapy recently, and todate no conception had occurred.

When 40 patients, who had failed to conceived by the above mentioned treatment schedules, were investigated further by laparoscopy or laparotomy and some with hormone profile it was found that 9 patients had pelvic factor (22.50%) and 2 patients had endocrine factor (5.00%) compromising fertility (Table VII). Pregnancy occurred following surgical treatment in 1 patient and administration of bromocriptine for hyperprolactinaemia in 1 patient.

TABLE V

Duration of Infertility and Registeration to Pregnancy Interval

Duration infertility	Registeration to pregnancy interval					
	1 to 6 months		7 to 12 months		more than 1 year	
	No. preg.	%age	No. preg.	%age	No. preg.	%age
1 to 2 years	62	72.95	21	24.70	2	2.35
3 to 4 years	45	76.28	12	20.33	2	3.39
5 years	9	75.00	2	16.67	1	8.33
above 5 years	17	85.00	3	15.00	nil	—

TABLE VI

Effect of Clomiphene Citrate on 'Unexplained Infertility'

Treatment Schedule	Total patients	Total pregnant	Percentage
Clomiphene therapy	127	45	35.43
No medication	365	131	35.89

Discussion

The usual practice is to begin infertility evaluations if the wife does not become pregnant within one year of marriage, with the couple staying together and having unprotected regular sex. The standard

TABLE VII

Laparoscopy/Laparotomy and Hormone Evaluation of 'Unexplained Infertility

Correctable pathology diagnosed	No. of patients	Treatment given	Pregnancy
Endometriosis—Stage I	2	Resection	nil
Endometriosis—Stage II	1	Resection	nil
Unilateral tubal block	1	Salpingo-oophorectomy	Pregnancy (normal delivery)
Inflammatory pelvic adhesions	3	Release of adhesions	nil
Peritubal adhesions	1	Salpingolysis	nil
Genital tuberculosis	1	Antituberculous	nil
Hyperprolactinaemia	2	i. Bromocriptine 7.5 mg/day	Pregnancy (12 weeks)
		ii. Bromocriptine 2.5 mg/day	Treatment continued

investigative protocol included history and examination of both partners, semen analysis, post-coital test, premenstrual endometrial biopsy (if possible BBT recording) and hysterosalpingography. We have considered a group of patients as having 'unexplained infertility' when the standard tests have failed to explain any cause. Is this 7 years' study of 2086 couples, our incidence for unexplained infertility is 23.58%.

Over a period of waiting and in some occasions with empirical treatment, 35.77% had achieved spontaneous conception. It means that 35% of women considered to be normal by the basic investigations could become pregnant without any form of further evaluation or treatment. Otherwords, these patients were 'normal' and probably required only an assurance with the basic investigations and proper advice on coital frequency to become pregnant in due course. This interesting observation clearly demonstrates the significant role of the simple investigations in infertility practice. Only when a contributory finding is obtained or patient fails to achieve a pregnancy after waiting we need consider elaborate, expensive and invasive investigative procedures.

Nonetheless, indiscriminate waiting for spontaneous conception after the standard investigations is also an unhealthy practice and is harmful to the couple. To some extent our study provides for indentifying the patients requiring detailed study, and to differentiate them from those who could afford to wait hopefully. The rate of spontaneous conception following investigations is around 40% in women who were upto the age of 30 years. But the concep tion rate was only around 18% between 31 and 35 years and 12% above 35 years. Moreover, only 9% of the total spontaneous conceptions have occurred in women aged above 30 years. For these reasons it is felt that elderly women above 30 years, irrespective of other factors, must undergo a comprehensive fertility evaluation.

Another factor that could influence the decision will be the duration of infertility. Again it is observed that the conception rate decreases with the duration of infertility. The conception rate which is as high as 49% for 1 year infertility, 45% for 2

years and 40% for 3 years has been reduced to 30% for 5 years and 20% after that period. Moreover, only 21 (11.93%) of the total 176 pregnancies were recorded in women with more than 5 years' infertility. Hence, irrespective of age, women with more than 5 years' infertility should have a detailed infertility work-up.

Our analysis reveals that 75 to 80% of patients with unexplained infertility are young (30 years or less) with an infertility duration of 1 to 5 years. The study indicates that these subjects could be hopefully followed for spontaenous conception to occur, if the standard investigations are noncontributory. Now the next question is how long to follow these patients without our further evaluations. Further scrutiny of the 176 spontaneous cinceptions reported shows that 75% of them have occurred within 6 months of registeration, and 97% within 1 year. The average registeration to conception interval was 4.60 months. Another interesting observation was that among the 92 pregnancies that have been recorded in women upto 25 years only 68% have occurred within 1 to 6 months and the rest 32% were after 6 months follow-up. Hence it may be stated that a 6 months period of optimistic waiting must be advocated in general, but if the patient is 25 years or less the period of waiting could be upto 1 year.

The harm of injudicious waiting with conservative approach as been rightly brought out by our laparoscopy/laparotomy evaluation and sometimes hormone evaluations performed in 40 patients with unexplained infertility. A correctable pelvic factor or endocrine disorder was diagnosed in 12 of these patients (27.50%). Specific surgical or hormone therapy resulted in prompt pregnancy in 2 subjects (18.18%).

We should mention that no form of empirical therapeutic modalities could futher improve the pregnancy rate in women with unexplained infertility. The conception rate was no better among the 127 women who were administered clomiphene citrate when compared with the control group. Fertility laparitomy yielded a very poor pregnancy rate of 16.66%. Eventhough recently started, Bromocriptine therapy in 12 subjects was not associated with a favourable outcome at the time of reporting.

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