THE PROGNOSIS FOR PATIENTS WITH UNEXPLAINED INFERTILITY

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ABSTRACT

The cumulative pregnancy rates in 70 couples with unexplained infertility was studied. A Life-table method of analysis was used. The overall cumulative pregnancy rates was 42% at 12 months and 48% at 24 months. A similar group of presumed fertile women who had stopped oral contraception for the sole purpose of becoming pregnant achieved these pregnancy rates by three months. Contrary to most other reports, our women with primary infertility had a better prognosis when compared to those with secondary infertility.

Keywords: Unexplained infertility, life-table analysis.

Introduction

Unexplained infertility continues to be an enigma. The true incidence in the general population remains unknown and the reported incidence in infertility clinics vary from 6%1 to 60%2. These differences between reports are probably due to the differences in population characteristics, extent of investigations and the criteria for its diagnosis. In addition, the reported prognosis for these couples varies considerably; overall pregnancy rates as low as 3% and as high as 60% have been reported3,4.

Most of the literature on this subject has been confined to Caucasian populations.

The aim of this study was to assess the characteristics and prognosis of couples with unexplained infertility in an Asian context, with particular reference to the Malaysian population.

Materials and Methods

The case records of 220 couples attending the Infertility Clinic, University Hospital, Kuala Lumpur from January 1985 to December 1987 were retrieved and analysed. One hundred and seventy records of couples who had completed their investigations were scrutinised to isolate those with unexplained infertility.

The criteria for inclusion were:
1. infertility for more than two years
2. coitus of at least 3 times per week
3. a semen analysis showing a volume of > 2ml, a concentration of > 20 x 10⁶ spermatozoa per ml, a % progressive motility of > 50% and a % normal morphology of > 50%.
4. ovulatory cycles as evidenced from a biphasic basal body temperature and a raised serum progesterone (day 21)
5. a normal serum prolactin level
6. a laparoscopy which showed normal pelvic findings. Tubal patency was also established during this procedure.

With the exception of a few patients who had an empirical course of clomiphene citrate, no definite treatment was given to these patients. After two years of follow-up, they were referred to private centres for assisted reproduction.

The cumulative pregnancy rates in these women with unexplained infertility was determined by the Life-Table method of analysis as described by Cramer et al⁵. Any patient who was lost to follow up was contacted to determine if she had conceived and if not, whether she was still attempting to conceive.

For comparison, the cumulative pregnancy rates in a group of 61 women who stopped oral contraception for the sole purpose of wanting a pregnancy was included (Fig 1). These women were presumably fertile.

### Results

Of the 170 couples investigated, 70 were classified as having unexplained infertility, thus giving an incidence of 41%. Forty-six (66%) had primary infertility whilst 24 (34%) had secondary infertility.

The median duration of infertility was four years. The age distribution of these women is shown in Table 1. More than 75% of the women with unexplained infertility were more than 30 years old.

<table>
<thead>
<tr>
<th>Age distribution (years)</th>
<th>Primary Infertility n (%)</th>
<th>Secondary Infertility n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>2 (3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>20 - 29</td>
<td>11 (16)</td>
<td>4 (6)</td>
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<tr>
<td>30 - 39</td>
<td>31 (44)</td>
<td>20 (29)</td>
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<tr>
<td>&gt; 40</td>
<td>1 (1)</td>
<td>1 (1)</td>
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An overall cumulative pregnancy rate of 42% at 12 months and 48% at 24 months was observed (Fig 1). Even though the cumulative pregnancy rates was promising in these groups, we made a comparison with the cumulative pregnancy rates in a group of 61 women who stopped oral contraception for the sole purpose of wanting a pregnancy (Fig 1). A significant difference was seen (p < 0.0005). These women (contraceptive users) achieved a similar pregnancy rate by only three months i.e. 55%. Therefore, it was assumed that there were some underlying factors which might have contributed to the subfertility in these groups of women.

Unexplained infertility is more because of under-mentioned factors than the proportionately high conception rate. The comparison between contraceptive and infertile women significantly assumed to have contributed to the reason.

It is hard to characterize exactly what contributes to infertility. It seems that the determination of the reason is vital in the investigation of infertility. Jaffe proposed a grading system for the diagnosis of primary infertility. The zona-free test has been proposed as a major test for the diagnosis of infertility. This test reduces the possibility of misdiagnosis; however, it may not be able to determine a specific cause of infertility.

Fig 1. Cumulative pregnancy rates in women with unexplained infertility and in women after stopping oral contraception.
secondary infertility (Fig 2); the cumulative pregnancy rates at 24 months in the 46 women with primary infertility was 52% whilst in the 24 women with secondary infertility it was 38%. However this was not statistically significant.

![Cumulative pregnancy rates in women with primary and secondary infertility.](image)

**Discussion**

Unexplained infertility should perhaps be more appropriately called subfertility because as our results show, a high proportion of our patients (up to 50%) do conceive over two years. However, when the conception rates in these couples were compared to a population of presumably fertile women (Fig 1), they were significantly reduced. It is therefore wrong to assume that there is no underlying factor contributing to their reduced fecundity – the reasons, however, remain unclear.

It is known that the greater the depth of investigation of these couples, the greater is its reduction in diagnosis. Coulam et al.9 and Jaffe et al.10 showed that by adding the diagnostic test of ultrasound monitoring of folliculogenesis, sperm antibody testing, zona-free hamster egg penetration assay and major histocompatibility typing, the diagnosis of unexplained infertility can be reduced by 60%. It must be realised, however, that most infertility clinics will not be able, as a routine, do what the authors propose.

In our group of patients, more than 75% were over 30 years old. Age may have contributed to their reduced fecundity. Collins and Rowe11 found that in their group of women with unexplained infertility, an additional year in the age of the patient, reduced her chances of pregnancy by 9%. Interestingly, contrary to other reports, the overall cumulative pregnancy rate in our women with primary infertility was better even though these patients did not receive any form of treatment. However this was not statistically significant. We were able to observe this because in our unit there were no facilities for assisted reproduction and the majority of our patients were left alone. These women need further evaluation to see whether there are any other contributing factors to the subfertility. Following the results in this study probably there is a place to leave these patients alone for one or two years before embarking on assisted reproduction, especially in young women.

Furthermore, that these patients may have a strong psychological overlay to their problem has been suggested. Adoption has been shown to improve the subsequent pregnancy rates in them7,12. However, the true causal relationship is difficult to prove.

There are now methods of assisted reproduction available that are directly applicable to these patients with unexplained infertility. Bearing in mind the good prognosis of these couples, the dilemma now is whether to discharge them from the clinic on the assumption that there are no underlying cause for their infertility or whether to institute these expensive and time consuming treatment modalities.

Murdoch et al.13, compared the cumulative pregnancy rates after gamete-intrafallopian transfer (GIFT) with the cumulative spontaneous pregnancy rates in couples with unexplained infertility. They showed that the chances of having a baby after one cycle of GIFT was significantly greater than the chance in a spontaneous cycle. However, they cautioned that for GIFT to be a
realistic form of treatment, more than one cycle should be offered.

The empirical use of clomiphene citrate for these patients has been another source for debate. Fisch et al\textsuperscript{14}, reported a double-blind, randomised prospective therapeutic trial of 148 couples with unexplained infertility. Treatment consisted of four consecutive cycles of either placebo or clomiphene citrate with and without human chorionic gonadotrophin (hCG) intra-muscularly. Whilst the placebo treatment resulted in no pregnancies over four months, clomiphene citrate was significantly better with a pregnancy rate of 19\% in those without hCG. In those who had hCG, the pregnancy rate was 7.6\% - a result not significantly better than that with placebo. The authors concluded that clomiphene citrate was useful in treating patients with unexplained infertility.

In conclusion, it appears that couples with unexplained infertility are definitely different from the normal fertile patients and perhaps by introducing extensive investigations the diagnosis can be narrowed down further. There’s a place for conservative management in young couples.

However, with the new methods of assisted reproduction the pregnancy rates in these patients with unexplained infertility may be improved. However the cost and resources involved must be borne in mind; especially since their spontaneous pregnancy rates are good.

References


