Efficacy of danazol treatment in infertile patients with endometriosis

A. Kulenthran, MBBS, MRCOG

Department of Obstetrics and Gynaecology, University Hospital, 59100 Kuala Lumpur, Malaysia

Summary

The study was done to assess the efficacy of danazol in the treatment of infertile patients with all stages of endometriosis. The cumulative pregnancy rates in 21 patients with Stage I and II endometriosis were compared to 21 patients with Stage III and IV endometriosis. Both groups had danazol treatment for six months. All other fertility related factors were controlled for in both groups. There was a cumulative pregnancy rate of 11% (standard error 7%) at 12 months of follow-up in the group with Stage I and II disease whilst it was 26% (standard error 10%) in the group with moderate or severe disease. These results question the validity of any classification system in prognosticating for fertility in patients with endometriosis.

Key words: Danazol, endometriosis, infertility.

Introduction

The mechanism by which endometriosis causes infertility are varied. In its severe form, its effects are predominantly mechanical with adhesion formation, distortion of pelvic anatomy, and the presence of endometriomata which affect folliculogenesis. Treatment is surgical. In its mild form, however, the reasons are more elusive. There is little or no distortion of pelvic anatomy and ovulation occurs normally. The need to treat these patient remains controversial.

Clinicians have therefore realised a need to categorise the disease by its severity so that there could be a rational approach to the problem. Various systems have evolved [1,2,3]. However most of these systems were either not comprehensive, lacked objectivity or did not prove to be sufficiently discerning.

To address the problem, the American Fertility Society (AFS) appointed a committee of nine experienced clinicians. From their discussions and deliberations, evolved the American Fertility Society Classification of Endometriosis (1979)[4]. It was based on a graded point system and the severity of the disease scored according to the natural progression of the disease.

Whilst the system had some advantages, defects became apparent with time. Because of this the AFS committee designed a new scheme, the Revised American Fertility Society Classification (1985)[5] again using a graded point system. The new system appeared to be objective, comprehensive and was precise in describing the severity of the disease. To–date it is the best working system we have.

Treatment of endometriosis with danazol, a 17–ethinyl–testosterone derivative was first reported by Grenblatt et al in 1971[6]. Early reports showed that it caused both gross resolution (regression) of the disease and enhancement of conception rates in infertile patients with endometriosis[7].

The present study was done to assess the efficacy of danazol in improving pregnancy rates in our group of infertile patients with all stages of endometriosis.

Patients and Methods

The cumulative pregnancy rates in two groups of infertile patients with endometriosis were compared. A cross-sectional approach was used and the data analysed in September 1990. The first included 21 patients with minimal or mild endometriosis (Stage I and II) and who were treated by danazol (600mg daily) for 6 months. The second included 21 patients with moderate or severe endometriosis (Stage III and IV) who were also treated with danazol (600 mg daily) for 6 months. The diagnosis of endometriosis was confirmed at laparoscopy and the disease staged according to the Revised AFS Classification 1985.

To exclude other fertility related factors that may have confounded the results, patients were included in the analysis only if they fulfilled the followed criteria:

1. infertility for more than 1 year
2. had evidence of ovulatory cycles as shown by a bi–phasic basal body temperature and a raised mid-luteal serum progesterone level
3. the semen analysis in their partners showed a concentration of > 20 million per ml with a motile fraction of > 50% showing progressive motility.
4. the fallopin tubes were confirmed to be patent at laparoscopy.

A post-coital test was not done in all patients because of its doubtful significance[8].

On completing danazol treatment, patients were followed up for 12 months to see if they had conceived. A life-table method of analysis of the cumulative pregnancy rates was used as described by Lamb and Cruz[9]. This method has the advantage of calculating the probability of pregnancy at any follow-up interval whilst it mathematically corrects for variable duration of follow-up. For those who had conceived, follow-up was defined as the time from stopping danazol to the last menstrual period before conception. For those who did not conceive, follow-up was for 12 months after stopping danazol treatment. Twelve months was chosen because it offered a compromise between giving the patient a chance at conception and the onset for recurrent disease following treatment – a recurrence rate of up to 47% within 12 months have been reported[10].

Statistical analysis for comparing the cumulative pregnancy rates was done using the z test[11]. Where appropriate elsewhere, the chi-square analysis was done.

Results

The patient characteristics with regards to age, parity and duration of follow-up in both groups is summarised in Table I. There was no significant difference seen for all these characteristics.

Within the 12 months of follow-up, 5 patients were lost to follow-up in the group with minimal or mild disease whilst in the group with moderate or severe disease, 3 patients were lost to follow-up.

There was a cumulative pregnancy rate of 11% (standard error 7%) at 12 months of follow-up in the group with minimal or mild disease whilst in the group with moderate or severe disease, the cumulative pregnancy rate was 26% (standard error 10%) (Fig. 1). This difference was however not significant; $z = 1.23$; $p = 0.2$.

Discussion

The results of this study show that the severity of endometriosis does not appear to affect the conception rates in our group of infertile patients who were treated with danazol. Care was taken to

Table I
Patient characteristics as regards age, parity and length of infertility

	Minimal or mild n = 21	Moderate or severe disease n = 21	Significance
Age (years)			
< 26	1	1	
26 – 29	6	9	
30 – 35	13	10	
> 35	1	1	
			$x^2 = 0.99$; p = NS
Parity			
nulliparous	18	20	
parous	3	1	
			$x^2 = 0.27$; p = NS
Length of infertility			
< 2 years	9	9	
2 – 5 years	9	8	
> 5 years	3	4	
			$x^2 = 0.2$; p = NS

x^2 chi-square; NS not significant

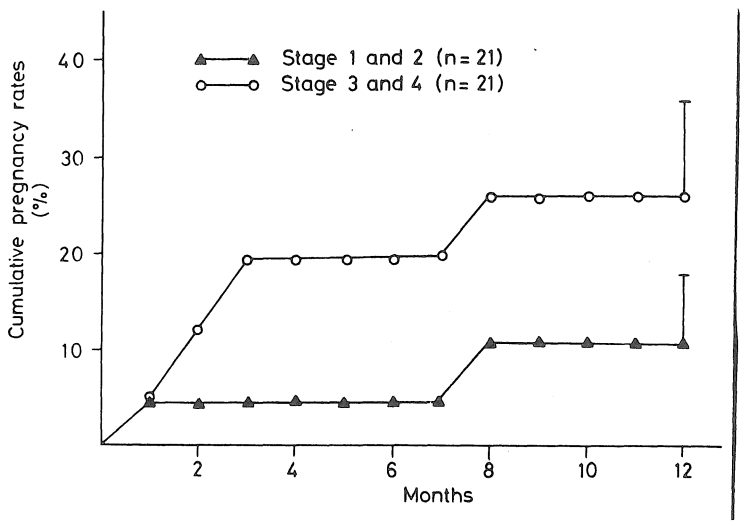

Fig. 1 Cumulative pregnancy rates in patients with Stage 1 and 2 and Stage 3 and 4 endometriosis

control for other fertility related factors such as the age of the patient, the length of infertility, and parity. Furthermore, patients with ovulatory disorders or those having a defective seminal analysis in their partners were excluded.

That there is an association between endometriosis and infertility is known but the effectiveness of treatment in improving pregnancy rates remains controversial. Although early reports show improved pregnancy rates with danazol treatment,[7] other studies with appropriate controls show no benefit of treatment in improving pregnancy rates over expectant management in patients with mild endometriosis[12,13,14]. This is so even when the treatment was shown to be effective[15].

Reports on pregnancy rates in patients with moderate or severe disease who were treated expectantly is sparse. Admittedly, to do this may have posed some ethical problems. Olive et al[16] showed a crude pregnancy rate of 21% in patients with moderate disease who were treated expectantly. Therefore, if this background pregnancy rates are considered, our results show that treatment does not improve pregnancy rates in patients with moderate or severe disease. It is possible therefore, that there are other as yet identified factors not related to the disease, that affects the conception rates in these patients with endometriosis.

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