Recent Advances in the Management of Infertility

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Preface

The field of Infertility or Reproductive Medicine is widely recognised as a subspecialty within the discipline of Obstetrics and Gynaecology. It has made enormous progress over recent years and will undoubtedly continue to do so with the development of the newer reproductive technologies.

In an endeavour to focus on the latest advances in this field, an international symposium on the "Recent Advances in the Management of Infertility" was organised in Singapore in 1988. Leading infertility specialists from various parts of the world came together and imparted the "state-of-the-art" in their respective areas of interest.

This book is the culmination of their efforts. The topics covered are far-ranging and comprehensive. Changing trends in the management of the infertile couple and idiopathic infertility are discussed in the earlier sections of the book. Difficult problems of ovulation and their treatment, including the use of LHRH agonists are then dealt with. This is followed by a discussion on the latest in the management of hyperprolactinaemia and endometriosis. The newer reproductive technologies in assisted conception are given full treatment, including ultrasonography in IVF, GIFT, laboratory IVF, cyropreservation of embryos and eggs, and the microfertilisation of eggs. Sperm dysfunction, antisperm antibodies, immunological infertility, and AID are also given detailed consideration. Finally, the roles of hysteroscopy and lasers are discussed.

It is hoped that this book may serve the needs of many medical practitioners in keeping abreast with the latest in infertility and its management. It is also anticipated that infertility specialists, generalists, and postgraduates in Obstetrics and Gynaecology may find this book of special interest and benefit.

Professor Christopher Chen
Chief Editor

Singapore, 1989

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Changing trends in the management of the infertile couple

J.F. Correy and J.K.R. Brodribb

Introduction

Prior to 1960, all patients with infertility had ovulation assessed by a basal body temperature (BBT) chart, a biphasic change indicating ovulation, a curettage or endometrial biopsy in the luteal phase of the cycle to demonstrate the appropriate histological transformation associated with ovulation and also the use of cervical mucus changes and vaginal exfoliative cytology. All these methods were used as there was no readily available hormone assay. Tubal function was assessed by hysterosalpingography (HSG) and in some cases practitioners were still using Rubin's test to demonstrate tubal patency.

Irradiation of the pituitary or ovary for ovulation induction was no longer acceptable. Diethylstilbestrol was given to "shock" the pituitary to release luteinizing factors or cortisone if there was evidence of androgen excess (Jeffcoate, 1962). Ovulation induction became a reality following Gemzell's work with human pituitary gonadotrophins (HPG) (Gemzell, 1958) and the use of clomiphene citrate (CC) by Greenblatt in 1961 (Greenblatt, 1961). It was several years before these drugs were to become available in Australia and the steroid assays, essential if the drugs were to be used, were able to be performed. It was not until 1966 that these modalities of treatment could be offered in Tasmania. That year also saw the commencement of laparoscopy in Australia.

Before the advent of gonadotrophins and CC, there was virtually no advance in infertility except perhaps in procedures to establish patency in blocked tubes. Pregnancies occurred after these procedures, as they did after HSG, Rubin's test, or spontaneously after the patient had seen the

practitioner. With the experience gained in the in vitro fertilisation (IVF) programmes in patients with clinically diseased and even blocked tubes, it is considered that the operative procedures may not have been as effective as previously thought. From 1983, when the IVF programme in Tasmania was started, 409 patients had 925 cycles of treatment, and 104 clinical pregnancies were achieved. There were, however, 105 spontaneous pregnancies, 54 prior to a treatment cycle and 51 after at least one failed treatment cycle. Approximately 60 per cent of these pregnancies occurred in patients with clinically diseased, and in a few instances, blocked tubes (Correy, 1988).

While there is no doubt that pregnancies do occur in relation to therapies, eg. Danocrine and surgical procedures in endometriosis, CC in ovulatory defects, AIH in mucus/semen problems, and surgical procedures in tubal disease, can it be assumed that such treatments and procedures are indeed as effective as we believe (Collins, 1983)? There have not been adequate controlled, randomised (and, if appropriate, double blind) trials in these conditions. Patients seek attention after a period of infertility and are investigated and treated. In 1971, Schokman and his colleagues (Schokman et al, 1971) pointed out the difficulties of assessing the efficacy of CC. In their series of 71 patients they considered suitable for CC (31 secondary amenorrhea and 40 oligomenorrhea with anovulation), 29 became pregnant on placebo tablets or during investigation.

The authors do not consider the modalities of treatment ineffective but consider that one should not be overconfident in the efficacy of various methods of treatment (Collins, 1983) until such can be shown in a controlled manner.

One problem any practitioner will have in determining pregnancy rates in various conditions, presumably causing infertility, is that patients default at various stages of investigation or treatment. Thus, one can give only the minimum pregnancy rates. Another difficulty in comparing pregnancy rates at various centres is in the criteria for treatment, and particularly the duration of infertility. Our policy, and we believe the policy in reputable centres, is not to investigate or treat infertility until 12 months have elapsed, unless there are pre-existing reasons for the infertility.

Materials and methods

The senior author (J.F.C.), with help from several colleagues, has conducted a Tasmania-wide service in infertility since 1966 in clinics in Hobart and Launceston. Initially, all patients, excluding those with tubal disease, were referred to the clinic, but as more specific modalities of treatment and a

wider range of investigations became available to general gynaecologists, the pattern of referral has altered (Brodribb, 1986). Consequently, a larger proportion of referred patients are those who have not conceived after CC or bromocriptine, or after failed insemination with partner's semen (AIH), or after more intensive investigation by the gynaecologists. Furthermore, there has also been an awareness by general gynaecologists in recent years that patients regularly menstruating may not be ovulating or may have ovulatory defects and increasing numbers of patients in this category have also been referred (Brodribb, 1986).

Computer forms for all patients who have become pregnant, moved interstate, transferred to the IVF clinic, signified they wished no further treatment, or have not attended for at least 12 months, have been completed and analysed. All patients currently being treated have been excluded from this study. Every patient's file was reviewed by the senior author (J.F.C.).

The menstrual status has been clinically grouped into the following categories: (a) primary amenorrhea, (b) secondary amenorrhea, (c) oligomenorrhea, (d) regular menses with no greater than six days variation in the cycle, (e) regular or irregular cycles with durations of greater than 35 days but not amounting to oligomenorrhea, and (f) frequent periods.

Although provision is made on the computer form for causes of anovulation or ovulatory defects, because the survey spans 22 years and diagnostic criteria have changed, no attempt has been made to categorise the causes in this manner.

The total number of new patients since 1966, excluding those currently being treated, was 1370. One hundred and sixty five were seen again after a pregnancy had been achieved, making the total number of infertility treatments 1535. One hundred and sixty patients were transferred to the IVF programme and will not be discussed further in this paper.

Only certain aspects of infertility, mainly illustrating trends, will be highlighted in this paper

Results

General features

During the period 1966 to 1987, 1535 patients were seen at the clinics with a complaint of infertility. Of these, 64.2 per cent were primary, and 35.8 per cent secondary infertility. The average ages were 26.6 years and 28.8 years (Table 1-1). Thirty-six patients did not have a designated date of first attendance. There were other patients seen at these clinics with

gynaecological endocrine disorders in whom infertility was not a factor, and for the purpose of this review have not been included.

When related to parity, 64.2 per cent were nulliparous and 33.8 per cent had one or two previous children. However, there were 30 patients who had previously had three or more children, but of these almost all had no children by the current relationship.

Infertility factors

Ovulatory disorders were the most common problems (69.5 per cent overall: 71.2 per cent for primary and 66.4 per cent for secondary infertility). Semen problems were the next most common, 28.5 per cent, while tubal factors accounted for 18.2 per cent of the patients. Mucus problems were found in 12.4 per cent; endometriosis in 5.2 per cent, and unexplained infertility in 1.1 per cent. The combined factors present were ovulatory/tubal factors 10.4 per cent, ovulatory/semen factors 19.4 per cent, and tubal/semen problems 3.8 per cent (Tables 1-2 and 1-3).

Non-attendance at the clinic

For the purpose of assessing the effectiveness of counselling by the staff, particularly the nursing staff, an attempt was made to identify those patients who failed to attend for further investigations, as against patients who elected to cease active investigation, moved interstate, or who were transferred to the IVF programme.

The distribution of infertility factors in the defaulters was similar to the general clinic population, with the exception of patients with tubal factors, in whom the default rate was lower. There was a marked reduction in the percentage of defaulters in the period 1982 to 1987 (Table 1-4).

Pregnancy rates

Overall clinic population

The total pregnancy rate, spontaneous pregnancy rate and the pregnancy rate as a result of specific therapy are shown in Table 1-5. There were a further 25 ongoing pregnancies achieved in 1987 which have not been included in the detailed analysis in this survey.

There is a significant spontaneous pregnancy rate (b of each category) in each of the infertility categories. Even in documented tubal disease, which included complete tubal occlusion at times, there is a spontaneous pregnancy rate from 13.0 per cent to 25.0 per cent.

The defaulters have not been excluded from these results and therefore the figures presented are a minimum pregnancy rate.

Early pregnancy outcome

This has been determined for only three main groups (Table 1-6), ie. ovulatory dysfunction, tubal disease and abnormal semen profiles. There were 81 patients in whom the outcome was not known.

The overall pregnancy rate was 51.7 per cent; ovulatory disorders 57.7 per cent; tubal disease 35 per cent and for semen abnormalities 40 per cent.

The spontaneous abortion rate of 14.7 per cent is higher than that for the community as a whole (9.0 per cent) (Correy, 1987). The overall multiple pregnancy rate was 4.4 per cent, with a rate of 4.2 per cent for those with ovulatory disorders.

Overall, in this clinic population, the ectopic pregnancy rate was 2.2 per cent for pregnancy > 20 weeks, whereas the ectopic pregnancy rate for Tasmania in 1986 was 1.1 per cent for pregnancies of greater than 20 weeks gestation. As expected, the highest ectopic pregnancy rate (8 per cent) occurred in patients with tubal disease.

Patients who had both laparoscopy and HSG

There were four groups comprising 227 patients who had both a laparoscopy and HSG performed. These groups were designated as both normal (group A): normal laparoscopy/abnormal HSG (group B); abnormal laparoscopy/normal HSG (group C) and both abnormal (group D) (Table 1-7).

The pregnancy rate of 45.2 per cent in patients with no abnormality (group A) was 7 per cent lower than that for total patients. The pregnancy rate for patients with demonstrated abnormalities in either the HSG or laparoscopy or both (groups B, C and D) was 40 per cent, which is only 11 per cent less than the pregnancy rate for the total series.

Menstrual status at first visit

The pregnancy rates are tabulated in Table 1-8. Forty-six per cent of the clinic population had regular menses (Category 4); 16 per cent had oligomenorrhea (Category 3); 17.8 per cent had secondary amenorrhea (Category 2), and 11 per cent had long cycles (Category 5). In Categories 3 and 5, ovulatory dysfunction was the major problem (86.6 per cent and 76.1 per cent with tubal and semen defects being of a similar incidence in these two categories. In those with regular menses, only 53.3 per cent had ovulatory

defects, with a greater proportion having tubal disease (26 per cent, and semen abnormalities (31.9 per cent).

The pregnancy rates in those patients with ovulatory dysfunction in Categories 2, 3 and 5 were similar and significantly higher (> 12 per cent) than those in the regular menses category. It would appear that this difference is due to the higher proportion of patients in this category having tubal disease and semen abnormalities.

When the ovulatory disorders were associated with either tubal or semen abnormalities, the pregnancy rates were significantly lower (Table 1-5). However, some caution is needed in the interpretation of these subgroups, as the numbers involved are small.

Discussion

There have been difficulties in the collation of data over a 22-year period. This is so because the changes in diagnostic tests, operative procedures and the understanding of the infertility disease processes, combined with the advent of newer modes of therapy, have made the concept of uniformity in investigative and therapeutic processes impossible. As such, we accept it is not possible to apply the rigorous controls that are now becoming widely accepted by clinicians as necessary to interpret the success or otherwise of the various treatment modalities (Lillford, 1987; Olive, 1986).

However, it is possible to analyse the broad experience over 22 years. We have included in our total patient population those patients who defaulted (and hence would tend to reduce the pregnancy rates) as well as other patients who, for one reason or another (poor attendance etc.), we would ideally prefer to exclude as they do not reflect the results of sustained investigation and treatment.

As shown by our results, it is disappointing that for the clinic population, in certain respects such as total pregnancy rates, there has been no change over 22 years (Table 1-5, line c of "overall"). In other areas such as in the defaulting population (Table 1-4), there appears to be a reduction in defaulters occurring toward the latter part of the period of investigation. Finally, we have demonstrated that the continuation of certain procedures, eg., HSG, would not appear to be justified for routine investigation of tubal function, a conclusion others have commented on in recent times (Randolph, 1986; WHO Taskforce, 1986).

In assessing couples with infertility, reliance is placed on published series indicating the relative proportions that each factor contributes towards the overall problem of infertility. This has guided us in a sequence

of investigations to allow a maximal detection rate. However, it is necessary that local figures are assessed so as to avoid unnecessary investigations on couples.

Such an example comes from our state where Correy and Schokman (1977) demonstrated, when investigating anovulatory and secondary amenorrheic patients, four of 58 HSG's were abnormal but that with ovulation induction three of these patients became pregnant. Only one of 60 patients who had a laparoscopy had a potentially treatable tubal condition, the implication being that assessment of tubal function was not an essential early investigation in such patients as had been suggested in the past. As well, it only confirms the opinion of others that, although there may appear to be significant tubal disease including bilateral occlusion, pregnancy occurring spontaneously cannot be discounted (Gomel, 1981; Correy, 1988).

In this discussion we will highlight a number of areas that appear to be important to our practice and indicate changing trends in the management of some aspects of infertility. We will not include the more sophisticated and specific regimens of treatment with human menopausal gonadotrophins, follicle stimulating hormone, GnRH infusion or analogues etc., but will refer to these only in the suggested protocols of management.

Infertility factors

It is apparent that in our clinic population there is a very high incidence of ovulatory dysfunction, 69.5 percent overall, and this is so for both primary and secondary infertility. Overall, in both primary and secondary infertility, there is no significant difference in the proportion of other factors, including combined etiological factors. On the basis of previously published data, our expectation would have been for a lower incidence of ovulatory disorders (Hull, 1985; Thomas, 1980; Cox, 1975). Hull et al. reported 21 per cent as having ovulatory failure, Thomas and Forrest in Melbourne reported 50.2 per cent while our incidence is 69.5 per cent. This lends further support to the assertion that it is important to assess the local population in order to understand where the required attention is needed.

The incidence of 20 per cent tubal factors is higher than the 6.5 per cent to 14 per cent reported in other series (Hull, 1985; Thomas, 1980; Cox, 1975). There is a slightly higher incidence of tubal factors in our primary infertility population, 22.9 per cent in primary infertility compared to 20.4 per cent in secondary infertility. Thomas and Forrest in Melbourne also reported a slightly higher incidence in primary infertility, 7.8 per cent as compared to 4.5 per cent.

Semen abnormalities accounted for 28.5 per cent of the overall factors in this series. This compares with 21 per cent (Hull, 1985), 6.2 per cent (Thomas, 1980), and 19.7 per cent (Cox, 1975). Since 1986 we have as a routine investigated male and female partners for antisperm antibody status using the immunobead test. Of a total of 191 men, 11 (5.8 per cent) had significant sperm head attachment of IgG (> 50 per cent). This is similar to reported figures by Harding et al. (1987). The antibody status was also determined in the serum of 183 women and, of these, 3.8 per cent had sperm head attachment of IgG in significant levels (> 50 per cent). Immunological factors would appear to play an important part in infertility, but at this time the status of immunological aspects of infertility, while being intensively investigated, has yet to be fully clarified, particularly in relation to therapeutic procedures, one of which (steroid therapy) is not without significant risks.

The whole subject of antisperm antibodies is unclear because (a) antibodies may occur in the serum of children, (b) they may transiently appear in both males and females, (c) pregnancies may occur in the presence of immobilising antibodies, (d) in vitro fertilisation occurs but pregnancies in patients with immobilising antibodies, particularly in the female, are rare, (e) the post coital test may still be reasonable, and (f) inconsistency in detection of antibodies in various laboratories (Bronson, 1985). At this stage the authors consider that AIH is not helpful in the presence of significant antibodies in the female.

Trends in infertility factors in the clinic population

In Table 1-3 there is a summary of infertility factors given as a percentage of the annual number of patients attending the clinic. It can be seen that overall numbers of patients attending the clinic had progressively increased but there appears to be a reduction in this trend in the last two years. This is probably due to the ready availability of CC to general gynaecologists and the aforementioned changing pattern of referral.

Over the 22 years there has been a gradual reduction in the proportion of ovulatory disorders. This can be explained in several ways. Firstly, the treatment of ovulatory disorders by general gynaecologists with CC. Secondly, the clinic was set up to manage ovulatory disorders, hence it is not surprising that 85 per cent of patients were initially in this category. However, as the clinic developed there were, and are, referrals for other reasons with a consequent dilution effect. Diagnostic methods for ovulation and its disorders have improved, so that we no longer rely on vaginal cytology, cervical mucus and BBT charts to determine ovulation. Basal body temperature

charts have been shown to be a poor predictor of ovulatory events (Lenton, 1977; Schokman, 1977), but do have a role in determining the length of the luteal phase, timing of coitus, and timing for various investigations and treatments, and as such are continued in many centres.

Coincident with the fall in percentage of patients with ovulatory dysfunction, there has been an increase in the percentage diagnosed as having tubal disease. This is due in some measure to the more regular use of laparoscopy to assess both tubal and pelvic factors. In 1966, laparoscopy was introduced into gynaecological practice in Australia and since then reports have appeared on its place in investigative gynaecology (Blunt, 1972; Correy, 1973). Even the senior author (J.F.C.), who in 1973 questioned the changing trend to laparoscopy instead of HSG in the investigation of infertility, considers that time has shown HSG is too unreliable in the determination of tubal disease and indeed this has been borne out by our own experience and the experience of others (Randolph, 1986; WHO Taskforce, 1986; Drake, 1980).

Attendance at the clinic

As can be seen from Table 1-3, the patients who ceased attendance of their own volition, as against those who moved from the state or were transferred from the general infertility clinic to the IVF clinic, remained steady at about 27 per cent to 30 per cent until 1981. However, from 1982–1987 the defaulters rate has fallen to 21 per cent and in 1986–87 10 per cent. Most of these have been patients seen at the Launceston clinic. We have considered that the basis of good infertility clinic care is the concept of day to day care, emotionally as well as with regard to the ongoing investigation and treatment. Since 1983 the Hobart clinic has had the services of a fulltime nurse coordinator who, with her staff, has come to know the patients very well and has provided a continuing seven days a week service, including counselling, to the couples. The authors consider that the fall in the rate of defaulters reflects the provision of this service. Since 1983 the services of the nurse coordinator have also extended to one of the author's (J.F.C.) private patients. Of 152 patients, only seven have defaulted, which is further evidence of the value of such a service.

Non-attendance is always a problem because it represents failed effort and a lack of communication and also a loss of investment by the health system, as well as a reduction in the potential for pregnancy. In 1986, Brodribb and his colleagues (Brodribb et al, 1986) were able to show that defaulters who had regular cycles had a pregnancy rate of 40 per cent, whereas the pregnancy rate for those continuing to attend the clinic was 55 per cent. Thus, non-attendance reduced the chance of pregnancy by a third. As has