THE AETIOLOGY OF INFERTILITY IN 1162 INVESTIGATED COUPLES

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Summary: The aetiological factors associated with 1162 couples who attended a single infertility clinic and who were assessed according to a fixed protocol over an eight-year period were analysed retrospectively. Male problems accounted for 17 per cent, ovulation disorders 31 per cent, tubal factors were present in 18 per cent and idiopathic infertility was observed in 32 per cent. Single factor infertility was present in 58.8 per cent and multiple factors were present in 9.8 per cent of all cases.

Although results may be biased by sub-speciality interests, only by continuous updating with reference to the most modern accepted methods of investigation can the likely demand for specialised infertility services and *in vitro* fertilisation be determined with accuracy.

INTRODUCTION

The Committee of Inquiry into Human Fertilisation and Embryology, chaired by Dame Mary Warnock (1984), recommended expansion of infertility services and the provision of 'in-vitro' fertilisation. There is a paucity of information about couples who have been thoroughly investigated using modern accepted diagnostic techniques, because the majority of infertile couples are seen at routine gynaecology clinics (Barnes, 1985) and the advances in diagnosis and therapy over the past few years have made it difficult to collect meaningful statistics.

All patients attending the Infertility Clinic at Glasgow Royal Infirmary have been investigated according to a fixed protocol for over ten years and retrospective computerisation of all infertility records has allowed statistical assessment of these couples.

PATIENTS AND METHODS

The case records of 1162 couples attending the Infertility Clinic from 1975 to 1983, and who underwent basic assessment (table 1), were analysed retrospectively. All patients who were not specifically complaining of sub-fertility, who failed to re-attend the Clinic after an initial visit, or who were pregnant at their first visit or before completion of investigations, were excluded. Any secondary referrals who had been incompletely assessed elsewhere underwent completion of basic investigations within our Unit.

Amenorrhoea was defined as lack of menstruation for at least six months and oligomenorrhoea as menstruation at an interval of not less than 42 days. Ovulation was determined by a mid-luteal plasma progesterone level of >30 n·mol/l. Laparoscopy was the primary method of choice for tubal assessment. All patients who had unilateral or bilateral tubal damage, ranging from patency with peri-tubal adhesions to gross hydrosalpinges, were included in the group with tubal problems. Endometrial tissue was sent for histology and culture for tubercle bacilli, but from 1983 onwards biopsy was only undertaken if there was evidence of tubal damage.

Seminal analysis was repeated if an initial sample failed to attain Health Organisation standards (count $>20\times10^6$/cc, motility >40 per cent, agglutination <10 per cent).

More detailed investigations were arranged when seminal results remained below this standard.

RESULTS

Primary infertility accounted for 822 (707.7 per cent) and secondary infertility for 340 (29.3 per cent) couples.

Principal and secondary factors are shown in table 2 and 3. The majority of patients had unifactorial infertility, more than one significant factor being present in only 10.3 per cent of those with primary infertility and 8.8 per cent of those with secondary infertility. In assessing

Table 1. — *Infertility assessment.*

Semen analysis/referral if necessary
History, examination, smear and swabs
Plasma, F.B., L.H., F.S.H., Prolactin, Progesterone, 17^{B} oestradiol, T.3, T.4, and rubella screen
Luteal progesterone, testosterone and 17^{B} oestradiol
Laparoscopy/hysterosalpingogram

those cases with multiple factors experienced judgement was sometimes necessary to determine the principal aetiological factor.

In the primary infertility group ovulatory problems accounted for 271 (32.9 per cent) of all the principal factors and were implicated in a further 61 (7.4 per cent). Five patients had premature ovarian failure. Tubal damage was thought to be the principal factor in 112 (13.6 per cent) of cases, although in seven of those there was extensive unilateral damage only. Six patients, all of whom demonstrated tubal damage, had endometrial tissue showing active tuberculosis. Similarly, in the group with secondary infertility ovulatory problems accounted for 88 (25.9 per cent) cases and were implicated in a further 25 (7.2 per cent). Four patients had premature ovarian failure. One patient with hyperprolactinaemia had a pituitary macroadenoma surgically removed.

Tubal problems were present in 103 (30.3 per cent) cases, two patients having unilateral damage and two patients active tuberculosis. Four male partners with azoospermia in this group had unproven fertility.

The majority of couples presented with at least two years of infertility (table 4). In general, the patients who presented earliest were those with overt symptoms suggestive of abnormal endocrinology. The majority of women presented before the age of 30 years (table 5). The average age of the female partner in the group with primary infertility was 27.10 (±4.5 SD) years, but where the principal factor was endometriosis 34 per cent presented in the age group of 31 to 35 years. The average age of the female partner in the group with secondary infertility was 28.07 (±4.5 SD) years.

DISCUSSION

On reviewing previous studies of large numbers of infertile couples (Cox, 1975; Katayama *et al.*, 1978; Templeton and Penney, 1982; Collins *et al.*, 1983) there

Table 2. — *Aetiological factors associated with secondary infertility (n = 340).*

Principal factors		Secondary factors					
		Suspect Male		Oligomenorrhoea		Endometriosis	Combined Oligomenorrhoea and Suspect Male
	Number (%)	Number	(%)	Number	(%)	Number (%)	Number (%)
Azoospermia	35 (4.2)						
Suspect Male	95 (11.5)			35	(4.2)	6 (0.7)	
Tubal Infertility	73 (8.8)	13	(1.6)	23	(2.8)		3 (0.4)
Primary Amenorrhoea	8 (1)	1	(0.1)				
Secondary Amenorrhoea	60 (7.3)	1	(0.1)				
Oligomenorrhoea	159 (19.3)						
Endometriosis	17 (2.1)						
Anovulatory Regular Cycles	42 (5.1)						
No abnormality	249 (30.1)						

Table 3. — *Aetiological factors associated with primary infertility (n = 822).*

Principal factors	Number (%)	Secondary factors: Suspect Male Number (%)	Secondary factors: Oligomenorrhoea Number (%)
Azoospermia	4 (1.2)		
Suspect Male	17 (5)		6 (1.6)
Tubal Infertility	79 (23.2)	5 (1.5)	19 (5.6)
Secondary Amenorrhoea	33 (9.7)		
Oligomenorrhoea	52 (15.3)		
Endometriosis	6 (1.8)		
Anovulatory Regular Cycle	3 (0.9)		
No abnormality	116 (34.1)		

is seen to be a wide variation in the methods of assessment and the results thereby obtained. Many of these studies are from Centres which take secondary referrals and any specific interest of a particular clinic may bias results in favour of that interest.

Ovulation problems can account for up to 43 per cent of all cases (Cox, 1975) in clinics with a special interest to only 8.5 per cent where a separate clinic exists for endocrinological problems (Templeton and Penney, 1982). The Infertility Clinic in Glasgow acts as a secondary referral centre for further investigation and management of infertile couples who have not responded to simple therapy and also for couples who have no demonstrable abnormality on basic testing. Separate clinics also exist in the city for assessment of endometriosis and amenorrhoeic hyperprolactinaemia, although the majority of such patients are not complaining primarily of infertility. This may have biased our figures to some extent.

In our series, ovulation was determined by mid-luteal serum progesterone levels. Basal body temperature (BBT) and endometrial biopsy have been used extensively and sometimes exclusively by others as the method of ovulation assessment (Verkary, 1983; Collins *et al.*, 1983). BBT is only 80 per cent accurate in detecting ovulation (Lenton *et al.*, 1977), and biopsy may not reflect ovulation (Syer, 1978) and has been implicated in subsequent pelvic inflammation (Taylor and Graham, 1982) the formation of intra-uterine adhesions (Taylor *et al.*, 1981) and subsequent cervical incompetence (Anthony: personal communication). Endometrial biopsy is not now undertaken routinely in our Unit because of these reasons, although the prevalence of tuberculosis indicates the need for biopsy when tubal damage is noted.

As assessment of infertility advances with the advent of new techniques, this again influences results. Laparoscopy was

Table 4. — *Duration of infertility at presentation.*

	Primary Infertility (n = 822)	Secondary Infertility (n = 340)
≧ 2	165 (20%)	40 (11.8%)
>2 ≧ 5	493 (60%)	201 (59.1%)
>5 ≧10	115 (14%)	90 (26.5%)
>10	49 (6%)	9 (2.6%)

Table 5. — *Age of female at presentation.*

	Primary Infertility (n = 822)	Secondary Infertility (n = 340)
<30	649 (78.9%)	240 (70.6%)
31 - 35	138 (16.8%)	81 (23.8%)
>35	35 (4.3%)	19 (5.6%)

popularised by Steptoe (1965) and its benefits over other methods of assessing tubal function has been emphasized (Duignan *et al.*, 1972; Templeton and Kerr, 1977; Mursich and Behrran, 1982). The majority of previous studies have used tubal insufflation or hysterosalpingography as the primary method of tubal assessment but the preferred method for initial assessment in our series has been laparoscopy and hydrotubation. Duignan *et al.* (1972) reported evidence of tubal damage in 24.5 per cent of a group of patients with primary infertility and 34.8 per cent of a group with secondary infertility. In similarly assessed groups, Templeton and Kerr (1977) reported tubal damage in 21 per cent and 52.5 per cent respectively. We found a considerably lower incidence even taking into account those with unilateral damage only.

The incidence of male problems is similar to that of other series using standardised reference data, which may no longer be relevant. Recent innovative tests will require revision of attitudes to male infertility. Sperm motility, normality and fertilising ability are important in this context (Templeton *et al.*, 1982) and the zona free hamster egg penetration test (Yanagimachi *et al.*, 1976; Aitken, 1982) can be adjunct in the investigation of suspected male sub-fertility and unexplained infertility, as can the use of 'in-vitro' techniques, (Thounson *et al.*, 1980) although such tests are not yet widely available.

Previous studies have shown an overall incidence of cervical hostility of between one per cent and 17 per cent (Raymond *et al.*, 1969; Dor *et al.*, 1977; Drake *et al.*, 1977; Katayama *et al.*, 1978; Collins *et al.*, 1983). Post-coital testing was not carried out as part of our basic assessment because such tests require cervical mucus to be in the peri-ovulatory phase (Billings and Bennet, 1978) and simple methods of determining this phase are only 34 per cent accurate (Lenton *et al.*, 1977). There is also debate over the optimum timing of such tests (Tredway *et al.*, 1974; Hull *et al.*, 1982) and their interpretation (Jette and Glass, 1972; Kovacs *et al.*, 1978), although their value in predicting conception in otherwise normal couples has been shown (Hull *et al.*, 1982). It is our practice to carry out quantitative 'in-vitro' sperm-mucus penetration tests (Mathews *et al.*, 1980) using ultrasonic follicular assessment as a peri-ovulatory indicator of rising 17β oestradiol (Hackeloer *et al.*, 1979), but it is logistically impractical for us to carry out such tests, which require to be repeated if abnormal, except on patients with prolonged unexplained infertility. Preliminary results indicate abnormal sperm penetration caused by seminal plasma agglutinating antisperm antibodies, hostile mucus or lack of mucus in 22 per cent of those assessed.

Few studies have assessed multifactorial problems in the infertile couple, the majority concentrating on the principal factor involved' thus incorporating or excluding completely those couples with multiple problems. Verkary (1983) implicated a single factor in 53 per cent of his cases, two factors in 33 per cent and three factors in seven per cent. We failed to substantiate these figures, two factors being inmplicated in 9.5 per cent and three factors in only 0.2 per cent. This difference is likely to be associated with the 22 per cent incidence of endometriosis in the former series as opposed to two per cent in our series.

As investigations and treatment regimes become more complex, expensive and time-consuming, it is important to know the number of couples for whom they are relevant. In-vitro fertilisation has been reported as a successful method of treatment for tubal blockage, endometriosis, male factor infertility and unexplained infertility (Mahadevan *et al.*, 1983). We would emphasise the need for meticulous in-depth infertility investigation and pri-

mary treatment, as only in this way can innovative therapies be attempted (Check *et al.*, 1977; Fleming *et al.*, 1982; Asch *et al.*, 1984) which in the long-term may be simpler, cheaper and more beneficial than in-vitro fertilisation for many couples.

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