Effective HEALTH CARE

The Management of Subfertility

How effective are treatments for subfertility?

What would be the resource implications of a comprehensive service?

What organisational and management issues are important?

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- A comprehensive subfertility service for a population of 250 000 will result in around 230 referrals and may cost around £750 000 per year, including the additional costs for neonatal care.
- Purchasers should use maternity rates to compare the reported success of treatment centres, taking into account patient characteristics, length of follow up and numbers of treatment cycles.
- Drug treatment for women with absent periods (amenorrhoea) may restore fertility to near normal levels.
- Assisted conception techniques may be relatively effective for most causes of subfertility with a maternity rate of around 12% per cycle.
- Surgery is not effective for women with severely damaged fallopian tubes. In such cases resources would be more efficiently allocated to assisted conception.
- Provision of information and support is an essential component of high quality care and should be provided in all centres offering subfertility treatment.
- Districts purchasing subfertility services should agree guidelines for referral and treatment with specialist tertiary centres in order to enhance the continuity and quality of care and to keep tight contractual control on activity and costs.
- There is a need for well-designed randomized controlled trials to evaluate further the effectiveness of many treatments for different causes of subfertility.
- The decision whether to purchase subfertility services should take into account both the competing demands for scarce resources and the quality of evidence for effectiveness.

A BULLETIN ON THE EFFECTIVENESS OF HEALTH SERVICE INTERVENTIONS FOR DECISION-MAKERS

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A glossary of medical terms used is given in Appendix I (page 14).

A. NEED AND DEMAND FOR SERVICES

Two years of involuntary failure to conceive provides a useful definition of subfertility for the purposes of service planning. Up to 0.5% of women are likely to be referred for specialist services each year. This figure is likely to increase.

Size of the problem

A.1 It is difficult to estimate the extent of subfertility because of the variety of definitions used and poor data. After one year between 80-90% of couples attempting to conceive are successful, rising to approximately 95% after 2 years[1-4]. The time taken to conceive increases with age[3,5].

A.2 Failure to conceive after two years during which there has been sexual intercourse and no use of contraception is a useful definition for health service planning because of the high spontaneous conception rate after one year[6]. However, earlier access to specialist services may be indicated for some individuals where an underlying cause has been identified or because of increased age.

A.3 At any point in time the proportion of women of childbearing age experiencing subfertility (prevalence) is between 9 and 14%[1, 7-10]. Of these 70% have not conceived before (primary subfertility) and 30% have conceived (secondary subfertility) but do not necessarily have a child[11].

The *Effective Health Care* bulletins are based on a systematic review and synthesis of literature on the clinical effectiveness, cost-effectiveness and acceptability of health service interventions. Relevant and timely topics for review are selected by a Steering Group comprising managers, directors of public health and academics. Selection of topics takes into account the following criteria: resource implications, uncertainty about effectiveness, and the potential impact on health. The review and synthesis of the literature is carried out by a research team using established methodological checklists, with advice from expert consultants for each topic. The bulletins represent the views of the *Effective Health Care* research team.

A.4 A health authority (population 250 000 with 46 000 women aged 20-44 years) with an established subfertility service may expect around 230 (0.5%) new consultant referrals each year[6,11]. The need for subfertility services is likely to grow due to the trend towards later first pregnancies, and an increasing number of remarriages, and will be sensitive to changes in incidence of some sexually transmitted diseases.

A.5 Demand is increasing due to raised public awareness of treatment possibilities[12]. The estimate of need is higher than historical annual met demand of approximately 0.37% per year[6]. If services are expanded, planners should take into account hitherto unexpressed demand and the possible effect on demand, from women with secondary subfertility, of increased access to treatment. Need and demand will vary between populations according to the demographic, social and cultural factors.

The stress and distress of subfertility

A.6 There is some evidence that subfertility causes considerable emotional stress and distress in some couples, which affects many areas of their life[13-15]. Subfertility may result in social handicap preventing fulfilment of social roles and realisation of personal and societal expectations for parenthood[16].

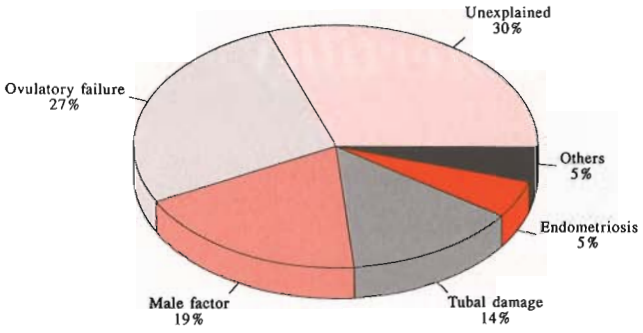

Figure 1 *Causes of subfertility.*

Sources: Hull *et al.*[11]; Haxton and Black[17]; Randall and Templeton[18].

Causes of subfertility

A.7 The approximate distribution of principal causes, based on studies of couples seeking treatment, are shown in Figure 1[11,17,18]. A significant proportion of couples will have more than one cause of subfertility. The distribution of causes differs between primary and secondary subfertility. The proportion of couples with subfertility categorised as unexplained will depend on the accuracy and extent of diagnostic testing[19-22].

A.8 There is no convincing evidence that psychological factors are a major cause of prolonged subfertility[23]. However this is a complex area which needs further study.

A.9 A small proportion of subfertility may be preventable, particularly some tubal damage, which may be caused by sexually transmitted diseases (eg *Chlamydia*)[24,25]. In order to assess the feasibility of preventive strategies better epidemiological studies are required.

B. EVALUATING THE EFFECTIVENESS OF TREATMENTS AND SERVICES

Purchasers should compare the reported success of specialist treatment centres on the basis of maternity rates, taking into account patient characteristics, length of follow up and numbers of treatment cycles.

Diagrams illustrating the effectiveness of treatments are shown in the text, and tables containing information about relevant studies are in Appendix II.

B.1 This bulletin reports the results of a review of the effectiveness of treatments and services for subfertile couples. Perceptions about effectiveness may influence the decision whether or not to purchase subfertility services[26]. The bulletin does not make recommendations about whether resources should be allocated to this area; this decision is not purely a technical issue, and will take into account the local circumstances and competing claims on resources.

B.2 There are difficulties in interpreting studies which look at the effectiveness of treatments, due to variability in outcome measures used, patient selection and spontaneous conception. For the same reasons it is difficult to compare the reported success rates of centres offering subfertility services. Therefore the following issues need to be taken into account when reading the literature, or when deciding from which centre to commission services.

Outcome measures

B.3 Ideally the management of subfertility should be evaluated according to the degree to which it has been successful in reducing the stress, distress or social handicap due to subfertility. This could involve, for example, measures of the extent to which treatment helps couples come to terms with their childlessness[15]. However this is difficult and there is a need for the development of valid and standardised measures of quality of life for research in this area.

B.4 *Reproductive outcomes* Most of the clinical literature concentrates on reproductive outcomes[27]. Several types of reproductive outcomes are used including: biochemical (evidence of) pregnancy, clinical pregnancy, ongoing pregnancy, births and maternities. This makes comparisons between trials problematical. Uniformity of outcome measures is required.

B.5 The most useful reproductive outcome for health care planners is the maternity rate, although this is rarely reported in the literature. The live birth rate overstates success because of the raised incidence of multiple births with some treatments. Other indicators such as conception rates or clinical pregnancy (which give more optimistic estimates of success) are useful indicators in scientific development and audit but are less relevant for health care planning[28]. Rates closest to maternity rates are presented in this bulletin.

Patient selection

B.6 Characteristics of patients such as age, parity, cause and duration of subfertility, and severity of pathology must be clearly stated as centres or treatments may appear either more or less successful because of variations in diagnosis and patient selection. To establish baselines for comparison, centres should also report the maternity rate of those on the waiting lists, where these exist.

Spontaneous pregnancies

B.7 A significant number of pregnancies will occur without treatment[29,30]. Effectiveness should be assessed on the basis of the maternity/pregnancy rate *over and above* the spontaneous pregnancy rate or else the impact of treatments will be over-estimated.

Analysis of results

B.8 Because the total (cumulative) chance of pregnancy increases with time and numbers of treatment cycles (see Figures 4-7), reports should include the length of follow up and the number of treatment cycles. Life table or survival analysis is being used increasingly, and can be a powerful means of comparison[2,31] if subjects in the original cohort are followed up throughout, or their loss *correctly* adjusted for to avoid biased estimates of effectiveness.

B.9 In order to be able to make a judgement as to which centres have better reproductive success rates, purchasers should seek clear information on outcomes, suitably adjusted for length of follow-up, number of treatment cycles and patient selection.

Quality of evidence

B.10 For many treatments the major evidence for effectiveness must be based on the outcomes recorded from large retrospective case series, compared with what is known of the spontaneous outcomes for untreated patients. This evidence is less reliable than that produced by a well-designed randomized controlled trial (RCT), controlled trial without randomization, cohort or case-control study[32].

B.11 Where there is substantial consistency between the results of large retrospective series between centres, over time and across countries this data can be used to give a broad indication of effectiveness. It must be stressed that these results might either over- or underestimate the effectiveness because of biases arising, for example, from patient selection.

B.12 Several treatments require more thorough evaluation by RCT using appropriate controls (such as a delayed treatment group) in order to obtain reliable estimates of the attributable increase in pregnancy and maternity rates. Attention should also be given to

assessing non-reproductive outcomes such as the well-being of couples.

B.13 The evidence for the effectiveness of each treatment presented in this bulletin is derived from populations. In the clinical management of individual patients this general information will have to be considered in conjunction with particular patient characteristics in order to determine the most appropriate course of action.

C. DIAGNOSIS OF THE CAUSE OF SUBFERTILITY

C.1 Preliminary investigations will result in a broad diagnosis in about 70% of patients. More detailed testing may then make the diagnosis more specific or attempt diagnosis in those so far unexplained.

C.2 The setting, content, and nature of diagnostic testing varies across the country. In practice there is little uniformity in the diagnostic criteria used for classifying patients. For further discussion see L.2.

C.3 There is uncertainty about the value of many tests in predicting the probability of patients benefiting from treatment. More research is needed to assess the prognostic value and cost-effectiveness of different diagnostic techniques and to develop protocols for their use.

D. PROVISION OF INFORMATION, SUPPORT, AND COUNSELLING

Active and sensitive provision of information and support is an important component of a high quality subfertility service.

D.1 The diagnosis and treatment of subfertility is often stressful[14,33-35]. This, combined with the psychological effects of subfertility, indicates an important role for information provision about both the implications of, and alternatives to, treatment for all subfertile couples in addition to support and therapeutic counselling for those who are particularly vulnerable.

D.2 The Human Fertilisation and Embryology Act (1990) and the guidelines of the Human Fertilisation and Embryology Authority (HFEA) obliges centres offering licensed treatments (IVF-ET and DI) to give information to all couples about the implications of treatment and to provide access to independent counselling for those who seek treatment.

D.3 Some of those undergoing subfertility treatment feel that there is a lack of provision for psychological and emotional needs[36-38]. The provision of information and emotional support for patients undergoing investigation or treatment for subfertility is an essential component of high quality care and should be provided in all centres offering subfertility treatment. Stress is reduced in those couples who feel involved in and in control of their treatment[39].

D.4 A number of models of support have been employed[14,40-42]. There has been little systematic study of the content of counselling, who should provide it, or the setting in which it should take place. Research is required to find the most effective means of providing support, and to better identify those who are particularly vulnerable and likely to benefit[43].

E. ASSISTED CONCEPTION TECHNIQUES

Techniques

E.1 Assisted conception techniques include artificial insemination, IVF-ET (*in vitro* fertilisation and embryo transfer), GIFT (gamete intrafallopian transfer), and other related techniques. Currently the most commonly practised is IVF-ET.

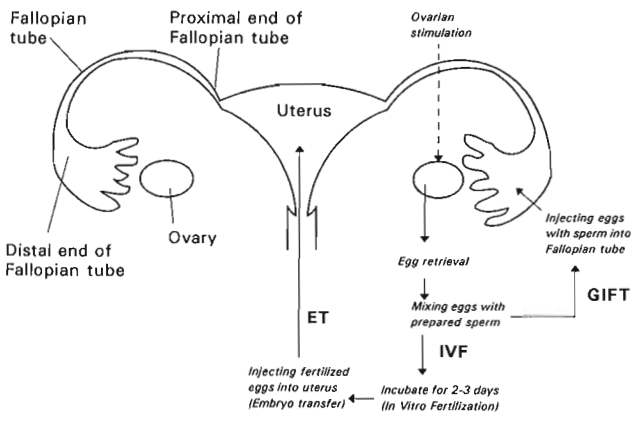

Figure 2 *Diagrammatic representation of female reproductive system and pathway of assisted conception.*

Overall effectiveness of IVF-ET

E.2 The Interim Licensing Authority (ILA) has been replaced by the HFEA which will continue to collect data on a statutory basis. HFEA (ILA prior to 1991) data is collected from all licensed centres in the UK for every new treatment cycle started. Pooling the data gives an average indication of the effectiveness of treatments across centres. In 1990 the average pregnancy rate with IVF-ET was 17% per treatment cycle[44]. This translates into an average maternity rate of 12% (per treatment cycle) and 14% per couple treated because some couples had more than one cycle. The average number of treatment cycles per patient in 1990 in the U.K. was 1.16[44].

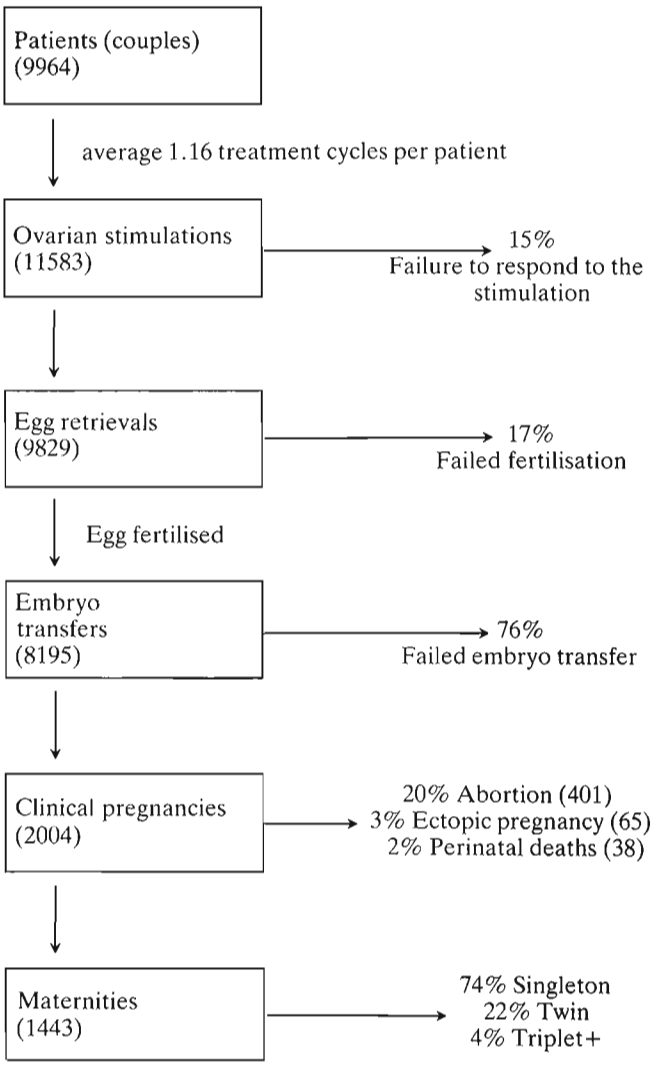

Figure 3 *The average reproductive experience of patients receiving IVF-ET.*
(UK data from 1990)[44].

E.3 The mean pregnancy and maternity rates from IVF-ET have been increasing steadily since 1986 but there are large variations across the country, with larger centres generally (but not always) having a higher success rate[44].

E.4 Since the patient characteristics are unlikely to be comparable, routine data on the reproductive outcomes shown in Tables 1 and 2, should not be used for direct comparison between GIFT and IVF-ET and between countries. Only specifically designed trials comparing treatments can reliably be used for this purpose.

Table 1 *Average pregnancy and maternity rates (%) of IVF-ET and GIFT, all causes, 1989 and 1990, UK.*

	IVF-ET				GIFT	
	Pregnancy		Maternity		Pregnancy	Maternity
Denominator	1989	1990	1989	1990	1989	1989
Patient	18	20	13	14	23	14
Treatment cycle	15	17	11	12	19	12
Egg retrieval	18	20	13	15	22	13
Transfer*	22	24	16	18	23	14

*Embryo transfer in IVF-ET procedure and gamete replacement in GIFT procedure;
Source: ILA 1991[45]; HFEA 1992[44].

Prematurity, multiple births and birth weight

E.5 24% of births after IVF-ET in England and Wales between 1978 and 1987 were preterm (before the 37th week of pregnancy) against a rate of 6% for natural conceptions[46].

E.6 Around 26% of deliveries were multiple births (22% twins and 4% triplets), compared with a natural rate of 1%[44-46], due to the transfer of several embryos per cycle. Multiple pregnancies are the main determinant of a poor outcome. To reduce the incidence of multiple pregnancy the HFEA requires that the number of embryos transferred at each cycle should normally be limited to three[44]. Some centres only transfer one egg per cycle, which reduces the risk of multiple pregnancy and the need for ovarian stimulation, but also reduces the probability of conception.

E.7 32% of these babies weigh less than 2500 g compared with 7% of all births; of these, 7% of babies weigh less than 1500 g compared with 1% for all births[46]. This is not entirely due to multiple and preterm births; full term singletons born after IVF-ET have a lower average birth weight than naturally conceived singletons[46].

E.8 Because of the raised incidence of multiple pregnancies and low birth weight, pregnancies due to assisted conception make increased demands on antenatal and neonatal services which have important cost implications (see K.6). Assisted conception is also associated with a higher perinatal mortality rate (19/1000 pregnancies and 26/1000 live births) compared with natural conceptions (8/1000 pregnancies and 16/1000 live births)[44].

Congenital malformations

E.9 The overall congenital malformation rate for babies born following IVF-ET is not raised[46-48]. Two studies have shown malformations of the central nervous system to be higher than expected, though the absolute number is too small to be conclusive[46,48], and it is not clear how

Table 2 *% Success rates by principal cause of subfertility, UK and USA, (1989 and 1990)*

	IVF-ET								GIFT					
	Pregnancy				Maternity				Pregnancy			Maternity		
(Per)	Cycle		Transfer		Cycle		Transfer		Cycle	Transfer		Cycle	Transfer	
Cause	1989	1990	1989	1990	1989	1990	1989	1990	1989	1989	1990	1989	1989	1990
Data from the United Kingdom:														
Tubal	15	18	20	24	11	13	14	17	17	19	23	7	7	14
Endometriosis	15	18	20	26	11	14	15	19	16	19	23	10	11	13
Male factor	15	16	21	25	10	11	15	17	19	21	24	12	13	17
Unexplained	14	15	21	22	11	12	17	17	20	23	22	14	16	15
Cervical factors	13	15	21	22	10	11	16	16	22	23	21	16	17	14
Ovarian & other	18	17	26	25	12	13	17	19	19	22	21	10	12	16
Data from the United States:														
Tubal			20				14			24			17	
Endometriosis			20				14			33			25	
Male factor			20				15			31			25	
Unexplained			23				20			33			26	
Female immune			24				14			35			23	

Note: UK data includes both partner and donor sperm for male subfertility.
Source: UK: ILA 1991[45]; HFEA 1992[44].
USA: MRI 1991[53].

much of this is explained by the characteristics of the couples seeking treatment, such as their age.

E.10 From the limited follow up it appears that if the neonatal period is uncomplicated, subsequent growth and development will be normal[49]. More research is needed to follow up children born as a result of assisted conception to assess the risk of problems later in life. Patient records should be stored for some time to allow retrospective (eg case control) studies to be conducted for this purpose.

Factors influencing success of IVF-ET

Characteristics of patients

E.11 The success of IVF-ET appears to decrease with factors including increased age of the woman (there is a marked decrease in success for women over 40)[44] and accurately diagnosed male factor subfertility[50-52].

E.12 Because a variety of patient characteristics affect the outcome of IVF-ET, reports of success rates from individual studies or centres may be more a reflection of policies for patient selection, rather than providing generalisable information on the value of the technique. However, pooled routine data, collected in the UK and USA, will be less liable to selection bias and therefore more generalisable. These show a consistency in success rates for different causes (Table 2). Whilst not reducing the need for properly controlled trials to further evaluate the effectiveness of assisted conception, this indicates that these data can be useful as working assumptions of likely success rates in initial planning exercises by health authorities who wish to purchase subfertility services.

E.13 In Table 2, rates based on transfers (ie following successful egg retrieval and fertilisation in IVF-ET or gamete replacement in GIFT) will appear higher than rates which are based on treatment cycles. The reported UK rates for male factor subfertility combine cycles using partner and those using donor sperm and so are higher than rates which report use of partner sperm alone. Because of the lack of consistency in the definitions and diagnosis of causes, treatments, lack of information on the selection of patients, and the greater number of embryos transferred per cycle in the USA, these retrospective data *cannot* be used to compare IVF-ET and GIFT, or make comparisons between countries and causes.

Learning curve

E.14 The success rate from assisted conception may improve with the experience of the centre and so volume of activity[54]. The smaller centres performing fewer treatment cycles a year report lower success rates on average than centres with a higher volume of work in 1990[44].

Recent advances

E.15 Recent advances such as 'pituitary down-regulation' to facilitate the scheduling of egg collection and enhancement of fertilisation, and the use of more accurate diagnosis of male factor using tests such as the sperm penetration test, are likely to improve the effectiveness of assisted conception techniques and identification of appropriate couples[51].

How many cycles?

E.16 The average number of treatment cycles per IVF-ET patient was 1.16 in 1990 in the UK[44] and 1.35 in the USA[53]. The per cycle conception and live birth rates appear to demonstrate a downward trend as the number of treatment cycles increases[52]. Patients discontinue treatment for a number of reasons such as unfavourable prognostic indications revealed in the first cycle, lack of finance, or stress. However, for the majority of couples with favourable indications the success rate is virtually maintained in successive cycles[51].

E.17 Whilst it may be medically appropriate to continue

treatment to help couples to accumulate an increasing chance of success, limitations of resources and considerations of equity may restrict the number of treatment cycles; three cycles is considered by experts in the field to be a reasonable limit. Other couples, with unfavourable indications, such as poor fertilisation, may be limited to only one cycle.

IVF-ET or GIFT?

E.18 GIFT is a more recent alternative to IVF-ET which requires that women have at least one patent and healthy fallopian tube.

E.19 An RCT comparing the effectiveness of GIFT and IVF-ET procedures showed no significant difference in pregnancy rates in the management of patients presenting with unexplained or male subfertility[21]. When the efficacy of IVF-ET and GIFT was compared for infertile couples with patent tubes in a RCT, IVF-ET was more effective than GIFT[55]. However some of those receiving GIFT had poor fertilisation which is easily detected with IVF-ET but not with GIFT. Indeed this is one of the problems of using GIFT without first demonstrating that fertilisation is possible.

E.20 A recent retrospective (though controlled) case series[56] indicates that GIFT is the treatment of choice for women with endometriosis and prolonged unexplained subfertility in couples in whom the ability to fertilise has previously been demonstrated using IVF. The success rates for GIFT in centres offering IVF was higher than that in centres offering GIFT alone[44]. However, properly designed RCTs are necessary to establish more precisely the relative effectiveness of these treatments (and others such as ZIFT) for different conditions and severities.

F. MALE FACTOR SUBFERTILITY

There is some evidence that medical treatments are of limited effectiveness for male factor subfertility. Assisted conception techniques can be effective.

Aetiology and diagnosis

F.1 Male cause of subfertility is diagnosed when sperm are either defective or absent. The underlying causes of male factor subfertility can be divided into two broad groups: those in which a specific cause has been identified, and those in which no underlying cause is found (idiopathic male subfertility).

F.2 The usefulness of semen analysis can be improved by examining sperm function in addition to numbers, shape, and motility. However, sperm function tests are not generally available. Their potential in determining more accurately the most appropriate form of treatment[51,58] needs more research.

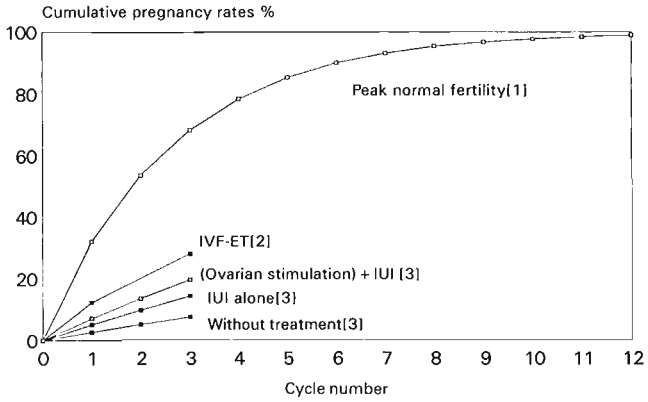

Figure 4 *Comparative cumulative pregnancy rates: male factor subfertility.*

[1] Biggers[57]
[2] Tan *et al*[52]
[3] Pooled data in Table A-2.

F.3 The *in vitro* fertilisation procedure itself (IVF) also has value in demonstrating the capacity of sperm to fertilise the egg in cases of suspected male subfertility.

Medical management

F.4 There is some evidence that the treatment of autoimmunity (the production of male antibodies to spermatozoa) with prednisolone as an immunosuppressant is effective. An RCT reported no pregnancy in couples treated with prednisolone and placebo for three months but patients with other causes of subfertility were included[59]. An RCT[60] found a higher pregnancy rate in couples treated with prednisolone but this was not statistically significant. A randomized cross-over trial showed a pregnancy rate of 27% for those treated compared to 7% for the placebo group[61] over a nine-month period. The potential side-effects of treatment with prednisolone include weight gain, cyclical skin rashes, aseptic necrosis of the femoral head and other serious side effects with high doses.

F.5 Various empirical treatments have been used to treat idiopathic male subfertility, clomiphene citrate being the most common. However, by integrating results from the three RCTs clomiphene citrate is shown to be ineffective (odds ratio = 1.03, 95% CI 0.51-2.07)[62-64].

F.6 Many other drugs have been used empirically to treat idiopathic male subfertility but controlled trials have shown these to be ineffective[65-72].

Surgical treatment

F.7 Several studies examine the effectiveness of testicular varicocele correction which may be an important factor in around 10% of males receiving treatment. The results are conflicting[73-77]: the RCT[76] showed no improvement but the result might be biased due to differential follow up. A well controlled trial with longer follow-up has shown a significant long term improvement in cumulative pregnancy rate (30% over 31 months for the treatment group, against 18% over 29 months for the control group)[77].

Assisted conception techniques

F.8 *IUI using partner sperm* Intrauterine insemination (IUI), is a technique in which prepared sperm are injected into the uterus. Based on the outcomes of ten controlled trials using partner sperm, the pregnancy rate of couples with diagnosed male factor subfertility was around 5.5% per cycle, that is 2.5 times that of the untreated group (95% CI 1.5-4.1)[78-87]. Most of these pregnancies occurred in the first four cycles of treatment[79,84,85,87,88]

F.9 *Donor insemination* Donor insemination (DI) is a widely accepted means of overcoming male factor subfertility especially where there are no sperm in partner semen (azoospermia) or sperm of 'poor quality'. The obligatory shift from fresh to cryopreserved sperm in DI programs because of the risk of HIV transmission has reduced the effectiveness of this procedure. A conception rate has been reported at 9% per cycle using frozen donor sperm in women without female factor or with corrected female factor[89-91]. Introduction of the sperm via IUI has been shown in RCTs to be more effective than intracervical insemination techniques[89,92]. A maximum of five treatment cycles is considered appropriate by experts in the field.

F.10 *IVF-ET using partner sperm* Although there are no controlled trials, large scale retrospective series indicate that IVF-ET appears one of the most effective treatments for male factor subfertility using partner sperm. The conception rate was around 6-10% per treatment cycle in IVF-ET with couples using partner sperm[51,52,93]. Rates are highest when the ability of the sperm to fertilise an egg has been demonstrated by IVF.

F.11 The practice by the ILA and others of combining results using donor and partner sperm in reports makes it impossible to use these sources for identifying the effectiveness of this technique using partner sperm only.

F.12 There is no reliable information on the effectiveness of GIFT in the treatment of male factor subfertility.

G. FEMALE FACTOR SUBFERTILITY: *TUBAL FACTORS*

Resources currently devoted to tubal surgery could be more efficiently used if reallocated to a more appropriate mix of tubal surgery for women with less severe disease and assisted conception for those with more severe pathologies.

Surgical techniques

G.1 The effectiveness of tubal surgery depends on the nature, site and severity of the tubal pathology, the extent and density of adhesions, the diagnostic measures employed, the techniques utilised, and the skill of the surgeon.

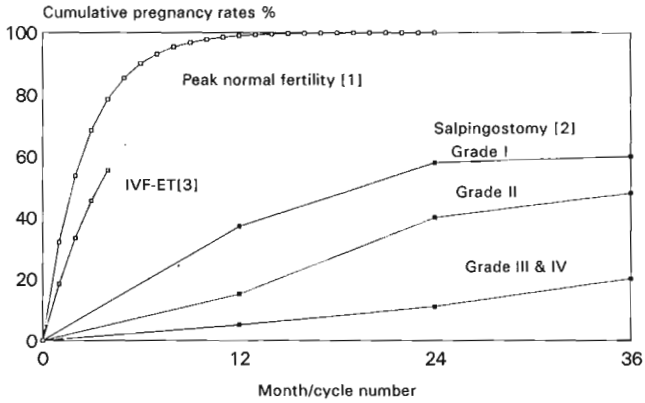

Figure 5 *Comparative cumulative pregnancy rates: tubal damage.*

[1] Biggers[57], [2] Donnez and Casanas-Roux[94], [3] HFEA[44].
The peak cumulative pregnancy rate takes much longer to achieve following tubal surgery compared to assisted conception.

G.2 *Site of tubal damage* There are no RCTs comparing surgery with no treatment. However there is evidence from extensive case series which may be compared with data on untreated tubal subfertility.

G.3 The most common site for tubal damage (80% of cases) is the *distal* end with birth rates after surgery around 20-30%, depending on severity[95-98]. 23% of all subsequent pregnancies are ectopic (outside of the uterus) which is associated with major maternal morbidity. The ectopic pregnancy rate is around 0.8% in the general population[99].

G.4 Surgery for occlusion of the *proximal* end has a live birth rate of 40-60%[100-102]. The ectopic pregnancy rate is around 8%. Some of this has been superseded by recanalisation techniques and trials comparing the two procedures are needed.

G.5 The birth rate for reversal of sterilisation varies from 50-80%+ by centre, and depends on the technique used for sterilisation[103-105]. This variation is partly attributable to patient selection.

G.6 *Severity of pathology* Patients with mild pathology and no adhesions (around 25% of patients) have much higher pregnancy rates (60%) three years after tubal surgery, which falls to about 15% for those with severe pathology[94,97,98,106-109] (see Appendix II, table A-1). However, due to the high spontaneous pregnancy rates in the very mild cases, the extra pregnancy rate attributable to the treatment is about the same (30%) for both mild and moderate grades (I & II) compared to only about 6% for more severe pathology[108].

G.7 *Diagnosis* In order to select patients with the best prognosis and to ensure that the most appropriate treatment is offered, expert preoperative assessment of the site, type and severity of tubal damage using both laparoscopy and hysterosalpingography (HSG) is advocated[97].

G.8 *Location of units offering tubal surgery* Term pregnancy rates achieved following tubal surgery for bilateral distal occlusion in non-specialist centres are

reported to be much lower (4%) than the rates generally shown in the literature which come from more specialist centres[110]. These findings should be interpreted with some caution in the absence of detailed information on patient selection in the different settings. However they raise doubts about the advisability of the routine practice of tubal surgery in non-specialist units.

Surgery versus IVF-ET (see Figure 5)

G.9 IVF-ET is an alternative to surgery since the technique bypasses the tubes (see Figure 2) and yields a pregnancy rate per cycle of 18% (13% maternity rate per cycle)[44].

G.10 The length of time between treatment and conception is longer following tubal surgery than IVF-ET[97]. Following salpingostomy, over 60% of intrauterine pregnancies occurred at least one year after surgery[111], whilst for reversal of sterilisation, the mean time to pregnancy is about 6 months[104]. However, an advantage of surgery over assisted conception is that a significant proportion of women who give birth after surgery go on to have more children without further intervention.

G.11 The choice between IVF-ET and tubal surgery is relatively clear when the tubal pathology is either mild or is severe, but more problematic for women with intermediate pathology.

G.12 Tubal surgery should not be undertaken for distal tubal damage without a clear indication that the severity of pathology is not severe. This should be part of a clear clinical protocol using one of a number of validated severity scales[106]. However for a substantial number of women with tubal subfertility surgery is not as effective as IVF-ET[112].

G.13 Resources currently devoted to tubal surgery could therefore be more efficiently used if reallocated to a more appropriate mix of tubal surgery for less severe disease and IVF-ET for the rest, resulting in a higher number of maternities. There is disagreement on the correct balance between the two[110,113] which can only be resolved by properly designed trials using a standard classification of severity.

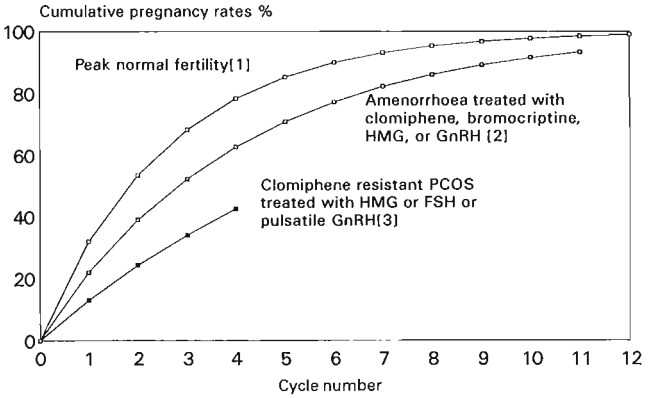

Figure 6 *Comparative cumulative pregnancy rates: anovulatory subfertility.*

[1] Biggers[57]
[2] Hull[114], Braat[116]
[3] Pooled data in Table A-3.

H. FEMALE FACTOR SUBFERTILITY: *OVULATORY DYSFUNCTION*

Medical treatments for ovulatory dysfunction caused by hyperprolactinaemic or hypothalamic amenorrhoea appear to be very effective, re-establishing fertility to near normal levels.

H.1 Failure to ovulate is normally indicated by the absence of menstruation (amenorrhoea) or infrequent periods (oligomenorrhoea). Ovulation is controlled by a complex interaction of hormones from the hypothalamus, pituitary and ovary (HPO axis). Treatments seek to remedy problems arising from imbalances in this axis.

H.2 There is good evidence that medical treatments are effective for anovulatory subfertility, especially where the specific problem in the HPO axis can be identified. Clomiphene citrate or if this fails gonadotrophin (eg. HMG) for hypothalamic dysfunction, and bromocriptine for hyperprolactinaemia, have been shown to restore fertility to near normal levels[114-116].

H.3 Treatments for ovulatory dysfunction caused by more complex hormonal dysfunction (eg. polycystic ovarian syndrome) are less effective, but may still be useful[116-123].

H.4 The increased rate of multiple pregnancy and other dangerous effects of ovarian hyperstimulation associated with the use of gonadotrophins may be avoided by the pulsatile administration of GnRH when medically indicated. A review of 16 retrospective studies indicates an average pregnancy rate of around 27% per treatment cycle[123]. The inconvenience of wearing the pump and the delivery system is compensated by the safety of treatment and the markedly reduced monitoring requirements.

I. FEMALE FACTOR SUBFERTILITY: *ENDOMETRIOSIS*

There is a significant level of spontaneous pregnancy among untreated women with endometriosis. Medical treatments have been shown to be ineffective. Surgical treatments also appear ineffective. For couples who have failed to conceive naturally, assisted conception techniques appear successful.

I.1 The relationship between endometriosis and subfertility is unclear. Many women with endometriosis conceive successfully without intervention[124] though

even mild endometriosis may result in subfertility[124-126]. Whilst there may be other non-reproductive indications for treatment, only those principally aimed at ameliorating subfertility are discussed here.

Medical treatment

I.2 RCTs have shown that the medical treatment of endometriosis using a variety of drugs such as danazol, medroxyprogesterone, nefarelin, gestrinone, or buserelin is **not** effective in increasing fertility[127-133]. Most studies have examined mild or moderate endometriosis. Research is required to evaluate the effectiveness of medical interventions for severe endometriosis.

Surgical treatment

I.3 Retrospective studies[134-136] and a poorly designed RCT[137] which make comparisons with danazol indicate that surgery is not an effective treatment.

I.4 Whilst one retrospective study has claimed that surgery in severe cases of endometriosis may raise fertility[138] this study was too small to make reasonable inference. Retrospective studies indicate that combinations of surgical and medical interventions are ineffective in mild endometriosis[135,139].

Assisted conception techniques

I.5 Retrospective data indicate a pregnancy rate up to 15-19% per cycle for IVF-ET and GIFT in endometriosis[44,45,52]. Maternity rates per cycle for IVF-ET of 14%[44], 15% (95% CI 10.3-21.2)[52] and 18% [56] have been reported. These rates are higher than would be expected from the ILA data, because the latter pools results from a wide range of centres. Success rates for severe endometriosis, which is less common, appear less successful[93].

J. UNEXPLAINED SUBFERTILITY

Assisted conception techniques appear the most effective treatment for unexplained subfertility. Medical treatments may have some effect upon maternity rates, and require further investigation.

J.1 A sizeable proportion of women with unexplained subfertility will not spontaneously conceive[140]. The chance of spontaneous conception falls progressively and prognosis is inversely related to duration of subfertility.

Medical treatment

J.2 A pregnancy rate of 5% per cycle in patients treated with clomiphene citrate has been shown, significantly higher than that in the placebo group[22]. In a randomized cross-over trial, clomiphene led overall to about a 50% increase in the pregnancy rate compared with placebo[141]. There is evidence from RCTs that both danazol and bromocriptine are not effective[142-145].

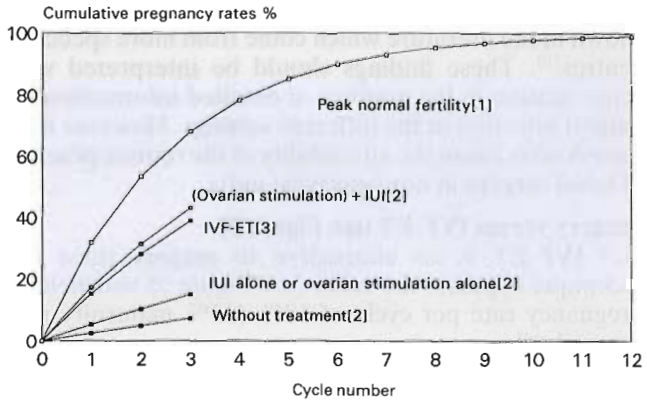

Figure 7 *Comparative cumulative pregnancy rates: unexplained subfertility.*

[1] Biggers[57]
[2] Pooled data in Table A-4
[3] HFEA[44]

Assisted conception techniques

J.3 *IUI partner sperm* Intrauterine insemination using partner sperm is not an effective treatment. An improvement in pregnancy rates of only 1.7% per month compared with an untreated control group has been shown[85].

J.4 There is some evidence that ovarian stimulation combined with IUI may be effective, though only for the first few cycles[20,87,146,147].

J.5 *IVF-ET and GIFT* A prospective controlled study[55] and several retrospective studies[52,56,148,149] suggest that pregnancy rates of 14-30% per treatment cycle can be achieved with IVF-ET. A 12% maternity rate per treatment cycle has been reported for couples with unexplained subfertility who were treated with IVF-ET in the UK[44].

J.6 A randomized controlled trial comparing GIFT and IVF-ET procedures found no significant difference in pregnancy rates[21] (see E.19).

K. COST-EFFECTIVE PURCHASING

K.1 Because economic appraisal of treatments depends upon estimates of effectiveness the problems which have been described in section B apply equally to cost-effectiveness estimates.

K.2 In addition, economic appraisal is difficult because of the common failure to report the construction of costings. Prices charged by providers do not accurately reflect resource use for a variety of reasons, such as cross-subsidisation and knock-on antenatal costs. Though purchasers are often interested in the price of treatments this may give a false impression of the true costs of activity and so result in less efficient choices. An attempt has been made to take these effects into

account, but the cost estimates presented here are approximate. Only treatments which have been shown to have some benefit are considered further.

K.3 The findings from the literature on effectiveness and costs have been supplemented with information from a confidential survey which obtained responses from nine specialist centres to produce rough cost estimates. Table 3 summarises the effectiveness of the various treatments for each cause of subfertility.

Table 3 *Consequences of subfertility treatments*

Condition and treatments	Increase in pregnancy rate per cycle (%)*	Multiple birth rate (%)	Side-effects
Ovulation disorders			
Amenorrhoea			
Clomiphene citrate	18	10	Minimal
Pulsatile GnRH	23		Minimal
Gonadotrophin	28	25	Hyperstimulation
Oligomenorrhoea			
Clomiphene citrate	18	10	Minimal
Gonadotrophin	3	30	Hyperstimulation
Hyperprolactinaemia			
Bromocriptine	28	—	Nausea
Tubal disorders			
Sterilisation reversal†	60		
Tubal surgery			
Grade I damage	27†	—	Stressful and anaesthetic risk
Grade II damage‡	30†	—	Increased risk of
Grade III damage	6†	—	ectopic pregnancy
IVF-ET	15	26	Stressful and anaesthetic risk
Endometriosis			
IVF-ET	14	26	Stressful and anaesthetic risk
Male Factor			
Autoimmunity			
Prednisolone	2	—	Moderate
General			
IUI (partner sperm)	3	—	
Superovulation-IUI	5	15	Moderate
DI (frozen sperm)	9	—	
IVF-ET	12	26	Stressful and anaesthetic risk
Surgery for varicocele	12†	—	Stressful and anaesthetic risk
Unexplained subfertility			
Clomiphene citrate	2.5	10	Minimal
IUI	1.7	—	
Superovulation-IUI	6.4	15	Moderate
GIFT	12	26	Increased ectopic pregnancy, stress and anaesthetic risk
IVF-ET	12	26	Stressful and anaesthetic risk

Notes:
*Pregnancy rate in excess of spontaneous pregnancy: for cyclical treatments these apply to the first few cycles of treatment but then diminish. Reducing these figures by 25 per cent gives a rough estimate of the maternity rate/cycle.
†Cumulative pregnancy rate after 2 years.
‡The added benefit of surgery for grade II severity appears higher than for grade I because of the higher spontaneous pregnancy rate in mild cases.

Cost of a subfertility service

K.4 A health authority with a population of 250 000 (46 000 women aged 20-44) with an established subfertility service may expect around 230 new consultant referrals each year (see A.4).

K.5 In order to illustrate the likely direct costs of this service Table 4 assumes the distribution of causes of subfertility given in Figure 1, the average number of cycles of treatment shown, and applies cost estimates of individual treatments. This table may be used at local level in conjunction with providers to produce estimates which correspond more closely to local requirements.

Effect on maternity and neonatal services

K.6 The increase in maternities resulting from treatment places an extra burden on general maternity services. Because these constitute a small proportion of the total maternities in a district their marginal cost will be very small[151] and is not considered further. The major resource implication for other services concerns the use of neonatal intensive care where it is generally perceived that there is under provision[152].

K.7 One hundred and eleven of the 230 district referrals are estimated to receive IVF-ET or GIFT treatments, of which on average 23 will result in a maternity (21%: taking into account some drop outs, a maximum of three cycles and a success rate of 12% per cycle). These 23 maternities will deliver 30 infants of which about two will have a very-low birth weight and about seven will have a low birth weight. Caring for very low birth weight babies is costly, and costs on average increase with decreasing birth weight[153].

K.8 A recent study conducted in the Yorkshire region[154] reported that admission to intensive care for ventilation occurred for 58% of very-low birth weight children and 7% of low birth weight children. This might underestimate needs since there was a suggestion that neonatal services were somewhat under-provided. The Simpson methodology[155], which provides a formula for the estimation of the total need for neonatal intensive care, assumes that 85% of very low and 20% of low birth weight babies will need intensive care for periods of 24 and 15 days respectively. This formula suggests these 30 babies will need an extra 65 days of ventilated intensive care.

K.9 The total need for intensive neonatal care for babies resulting from all treatments (see Table 4) as a result of treating the 230 referrals is estimated to be 120 days each year. There will also be some (smaller) knock-on costs due to the use of extra outpatient and inpatient antenatal care, special care baby units, and other paediatric and personal social services, which are difficult to estimate[153].

How much would this cost?

K.10 An upper limit on the additional neonatal services cost can be obtained by combining the estimate of total need with the cost of the most intensive care, for all

Table 4 *Illustration of costs based on a hypothetical scheme of subfertility management in a DHA with a population of 250 000.*
(excluding capital charges and administration)

Cause	Procedure (average number of cycles*)	Cost £	
		Per cycle†	Total
	230 diagnostic work-ups‡:	1 200	276 000
ovulatory failure (62)	51 treated with clomiphene citrate for 4 cycles	35	7 140
	11 treated with pulsatile GnRH for 3 cycles	450	14 850
	25 treated with HMG for 3 cycles	650	48 750
	11 treated with bromocriptine for 3 cycles	50	1 650
tubal damage (32)	8 treated with surgery	2 000	16 000
	24 treated with IVF-ET for 2 cycles	1 250	60 000
male factor (44)	6 treated with prednisolone for 6 cycles	30	1 080
	20 superovulation+IUI for 3 cycles	450	27 000
	28 treated with IVF-ET for 2 cycles	1 250	70 000
	23 treated with donor insemination for 3 cycles	150	10 350
endometriosis (12)	12 treated with IVF-ET or GIFT for 2 cycles	1 250	30 000
unexplained (69)	69 treated with clomiphene for 4 cycles	35	9 660
	58 superovulation+IUI for 3 cycles	450	78 300
	35 treated with IVF-ET or GIFT for 2 cycles	1 250	87 500
other cause (12)	12 treated with IVF-ET or GIFT for 2 cycles	1 250	30 000
Counselling	Service available for all patients		25 000
Total			793 280

Sources: Confidential survey of provider centres; Baird *et al*[150]; Lilford *et al*[112].
*The average number of cycles takes into account drop out during the course of treatment.
†Costs include monitoring where appropriate.
‡Including blood and urine tests, hormone assay semen analysis, laparoscopy, hysterosalpingogram, sperm function test, post-coital test, and hysteroscopy where indicated. Not all patients will have all these tests; the cost quoted takes this into account in calculating an average.

referrals. The average cost per day of this care can be estimated at about £600 (1992/93 prices) in major neonatal centres[156]. Therefore, the extra neonatal cost upon introducing a subfertility service is estimated as £72 000 pa. If subfertility services (especially those giving rise to multiple births) are currently being provided in the private sector some of these costs will already be borne by the NHS[153].

K.11 The total NHS cost of providing a comprehensive subfertility service for the 230 referred women can be estimated by adding in administrative and accommodation overheads and the extra neonatal care costs. This gives a total of just under £900 000 (Table 5). This total cost might easily be inflated if services are provided through the private sector although this will depend on the degree to which (monopsonistic) purchasers use provider competition to bid down costs.

Table 5 *Estimated budget for a district subfertility service.*

	Cost £ (1992)
Treatment cost[1]	793 280
Capital charges[2]	5 330
Administrative staff[3]	10 000
Neonatal service costs	72 000
Total	880 610

[1]including medical staff, counselling, drugs, and specialised equipment.
[2]annual equivalent cost, includes commissioning on-costs, furnishing and basic equipment, assuming 20 per cent of total capital charge for the clinic.
[3]including direct on-costs, assuming 20 per cent of the total administrative staff cost of the clinic.

K.12 There are two reasons why funding a comprehensive service might cost less. Firstly, health authorities already fund some medical and surgical treatments, although this is often contained within general service budgets and therefore to some extent hidden. In addition the NHS already bears much of the cost of the neonatal costs resulting from privately purchased assisted conception[153]. Secondly, some of the 230 couples referred will have a spontaneous pregnancy or will decide not to start a new treatment. Assuming an overall drop out (for either of these reasons) of around 15% the total cost to the purchaser falls to around £0.75 million per annum.

K.13 Health care commissioners will have to make decisions about the resources (if any) to devote to subfertility services within the wider context of district fertility services (including family planning) and competing demands for scarce resources from other sectors. This should also reflect the quality of the evidence for effectiveness of interventions.

L. ORGANISATION AND MANAGEMENT

L.1 If an authority decides to purchase subfertility services a number of organisational and management issues need to be considered.

L.2 In order to avoid unnecessary duplication of diagnostic testing and treatment and to reduce the stress

experienced by patients it is important that all providers of services to a given population agree on and adhere to a common management philosophy and framework. This is likely to optimise the continuity of care for individuals as they move between primary, secondary and tertiary levels of care.

L.3 For patients to be managed most effectively, and for resources to be used most efficiently, districts who wish to purchase for subfertility should have direct access to a comprehensive range of diagnostic and treatment services so that appropriate choices can be made.

L.4 There is a strong case for subfertility services to be provided predominantly in specialised tertiary units for the following reasons:

the management of subfertility is a complex task requiring skills not necessarily available in a district general hospital; these skills are more likely to be maintained where there is a sizeable volume of activity (see E.14);

if subfertility services are carried out at DGHs without specialist facilities, techniques (eg tubal surgery) may be offered because they are the only ones available, even when other treatments would have been more appropriate;

because of economies of scale, it is unlikely that a district centre, receiving 230 referrals a year could operate efficiently. It has been estimated for example that the most efficient treatment capacity for an IVF clinic is 750 started treatments a year[157,158]. This is close to the figures currently achieved by the large centres in the UK which on average saw 650 patients for assisted conception and provided 770 cycles in 1990[44].

L.5 Protocols for the management of subfertility for a district/FHSA population should be agreed with the tertiary centres with which contracts are placed. These protocols should address the roles of primary and secondary care in early management.

L.6 To treat couples too early leads to an inefficient use of resources due to the high spontaneous pregnancy rate. Therefore clear guidelines are required about appropriate criteria for the composition of the initial work-up and referral for use in primary care. A recent survey has indicated that GPs would welcome this (Kurinczuk J and Clarke M, University of Leicester; personal communication). The recent RCOG guidelines[159] and those developed by Professor Templeton at the University of Aberdeen (personal communication) could form the basis of such guidelines. These would be of value in helping to promote a more homogeneous and effective approach in practice, and should be incorporated into service specifications.

L.7 The role of secondary and tertiary providers in these protocols will need to take into account the expertise available locally, whilst trying to preserve continuity of care. This may result in a limited role for DGHs without specialist units.

L.8 When deciding how to distribute resources devoted to subfertility services both efficiency and equity need to be considered. One approach is to offer assisted conception to a selected group of women who are most likely to conceive. This may be efficient but inequitable in that a substantial proportion of women would be denied access to treatment. A more equitable but less efficient policy would be to offer all women access to at least one cycle where indicated.

L.9 Given the enthusiasm of providers and readiness of some couples to undergo many treatment cycles and any procedures offered, districts who do decide to purchase subfertility services need to keep tight contractual control over the volume of activity and the quality of care. Management guidelines are of central importance to achieving a cost-effective strategy.

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APPENDIX I

Glossary of terms

Amenorrhoea: Absence of periods.

Autoimmunity: presence of (male) antibodies to sperm.

Distal: Distant from (the uterus).

Donor insemination (DI): Use of prepared sperm from a donor in insemination.

Endometriosis: A condition where the lining of the uterus grows not only in its normal place, but also in others, such as around the tubes, ovaries or the outer lining of the pelvic organs.

GIFT: gamete intrafallopian transfer. Eggs are collected, and mixed outside the body with sperm from the partner. The egg/sperm mixture is immediately introduced to one or other fallopian tube. No attempt is made to ensure that fertilisation has taken place.

Hyperprolactinaemia: Overproduction of the hormone prolactin: a cause of amenorrhoea.

Hysterosalpingography: x-ray investigation of the tubes and uterus.

Intrauterine insemination (IUI): prepared sperm is introduced into the uterus, bypassing the cervix.

IVF-ET: *in vitro* fertilisation and embryo transfer. Medication is usually used to stimulate the production of eggs in the woman. Eggs are collected and combined with sperm outside the human body in the hope of fertilisation. After a period of around two days if fertilisation has occurred, embryos are transferred to the woman's uterus. In this way, IVF-ET effectively bypasses the fallopian tubes.

Laparoscopy: Minimally invasive surgical inspection of the fallopian tubes, ovaries and outside of the uterus.

Oligomenorrhoea: Infrequent periods.

Ovulatory dysfunction: Failure to produce eggs (oocytes).

Parity: The number of live births and still births at more than 28 weeks gestation delivered by a woman.

Proximal: Near to (the uterus).

Randomized controlled trial (RCT): Patients are randomly allocated to receive a treatment or suitable placebo in order to examine the effectiveness of a procedure. Well-designed RCTs provide the best evidence of the effectiveness of a procedure[32].

Salpingostomy: The operation performed to restore patency of the distal end of the fallopian tubes.

Superovulation IUI: IUI combined with medical treatment (ovarian stimulation) to increase the production of eggs.

Testicular varicocele: Enlargement of veins which drain the testis.

ZIFT: zygote intrafallopian transfer. Similar to IVF-ET, but the fertilised egg is reintroduced to the fallopian tubes, rather than the uterus.

APPENDIX II

Table A–1 *Time-specific intra-uterine pregnancy rates and total term pregnancy rates after tubal microsurgery at distal and fimbrial portion.*

Author	Procedure	Number	1yr	2yr	3yr	Total	Term Pregnancy
Donnez & Casanas-Roux 1986[94]	Salpingostomy						
	Grade I	132	37%	58%	60%	60%	
	Grade II	27	15%	40%	45%	48%	
,,	Grade III & IV	56	5%	11%	20%	23%	
	Salpingolysis	42	43%	62%	—	64%	
Godo *et al.* 1988[107]	Salpingostomy (All)	87	14%	20%	23%	23%	19%
	Grade I					46%	37%
	Grade II				19%	16%	
Wallach *et al.* 1983[104]	Salpingostomy (All)	24	4%	12%	21%	—	21%
,,	Salpingolysis	59	8.5%	24%	39%	39%	
Winston & Magara 1991[97]	Salpingostomy (All)	323	17%	28%	31%	33%	23%
Singhal *et al.* 1991[98]	Salpingostomy (All)	97	20%	—	—	34%	29%
	Grade I					46%	
	Grade II					27%	
	Grade III					14%	
Schlaff *et al.* 1990[109]	Neosalpingostomy (All)	95	15%	19%	—	20%	—
	Grade I					70%	
	Grade II					17%	
	Grade III					12%	
Laatikain *et al.* 1988[160]	Salpingostomy	93	9%	13%	16%	19%	13%

Average intra-uterine pregnancy rate from salpingostomy = 33% (mixed grades)
Average intra-uterine pregnancy rate from salpingolysis = 49%

Key to Tables A–2 to A–4

BC:	bromocriptine;	LH-RH-a:	luteinizing hormone-releasing hormone agonist;
Cause+:	means including other factors;	MT, PEN, TES:	mesterolone, pentoxifylline, testosterone;
CC:	clomiphene citrate;	NI:	natural intercourse;
CT:	controlled study without randomization;	OE:	ovarian electrocautery;
FSH:	follicle-stimulating hormone;	OS:	ovarian stimulation;
GnRH:	gonadotrophin-releasing hormone;	PCOS:	polycystic ovary syndrome;
HCG:	human chorionic gonadotrophin;	RCT:	randomized controlled study/(?indicates poor detail provided)
HMG:	human menopausal gonadotrophins;	SP:	spontaneous;
ICI:	intracervical insemination;	TIC:	timed intercourse;
IUI:	intra-uterine insemination;	USFA:	transvaginal ultrasound-guided follicular aspiration
IPI:	intra-peritoneal insemination		

Table A–2 *Studies of the treatment of male factor subfertility*

First author	Indications	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Ronnberg 1980[161]	Idiopathic oligozoospermia	RCT, for 3 mon, cross-over	CC, 50 mg, daily placebo	—	3/27 (11%) 1/29 (3%)
Micic 1985[162]	Idiopathic oligospermia	RCT? for 6–9 mon.	CC, 50 mg, daily observation	—	7/56 (13%) 0/45
Paulson 1979[163]	Idiopathic oligo-azoospermia	RCT? for 6–12 mon.	CC, 25 mg, daily cortisone acetate	—	7/20 (35%) 2/20 (10%)
Abel 1982[62]	Male idiopathic	RCT, 9 mon.	CC, 50 mg, daily vitamin C	—	15/93 (16%) 13/86 (15%)
Sokol 1988[63]	Male idiopathic	RCT, 12 mon.	CC, 25 mg, daily placebo	—	1/11 (9%) 4/9 (44%)
Wang 1983[64]	Idiopathic oligospermia	RCT, 6–9 mon.	placebo CC, 25–50 mg, daily MT, PEN, TES	—	0/7 8/29 (28%) 0/38
Wang 1985[164]	Idiopathic oligospermia	Review	CC, 25 mg, daily CC, 50 mg, daily	—	0/10 2/14 (14%)
WHO 1989[68]	Male factor	RCT, 6 mon.	Mesterolone Placebo	—	21/165 (13%) 7/83 (9%)
Hargreave 1984[67]	Male idiopathic	RCT 9 mon.	Mesterolone Vitamin C	—	34/176 (19%) 28/152 (18%)
Gerris 1991[69]	Idiopathic male	RCT 12 mon.	Mesterolone Placebo	—	7/27 (26%) 12/25 (48%)
Micic 1988[72]	Oligoasthenzoo. & genital infection	CT 3 mon.	Antibiotic/Kallikrein Antibiotic alone	— —	21/64 (33%) 10/56 (18%)
Micic 1985[165]	Oligoastheno- & asthenozoospermia	RCT?, 3–6 mon.	Kallikrein No treatment	—	9/45 (20%) 0/30
Izzo 1983[166]	Male	RCT, 3 mon.	Kallikrein Placebo	—	3/15 (20%) 0/15
Comhaire 1986[167]	Male accessory infection	RCT, 1 mon.	Doxycycline Placebo	2/107 (2%) 1/68 (1%)	2/20 (10%) 1/13 (8%)
Hovatta 1979[71]	Oligospermia	RCT, 12 weeks	Bromocriptine Placebo	—	1/20 (5%) 2/20 (10%)
Clark 1989[70]	Idiopathic oligozoospermia	RCT, 8 mon. cross-over	Testolactone Placebo	0/200 0/200	0/25 0/25
Comhaire 1990[65]	Idiopathic testicular failure	RCT, 3 mon.	Testosterone-undecanoate Placebo	—	1/24 (4%) 1/25 (4%)
Pusch 1989[66]	Oligozoospermia	RCT, 100 days	Testosterone-undecanoate Placebo	—	6/30 (20%) 4/30 (13%)
Hendry 1990[61]	Antibodies to spermatozoa	RCT, 9 mon. cross-over	Prednisolone Placebo	—	9/33 (27%) 2/27 (7%)
Haas 1987[60]	Sperm-associated antibodies	RCT, 3 mon.	Methylprednisolone Placebo	—	3/24 (13%) 1/19 (5%)
Bals-Pratsch 1992[59]	Sperm antibodies (? other causes)	RCT, 3 mon. cross-over	Prednisolone Placebo	—	0/19 0/19
Tredway 1990[168]	Male factor	Review	(SP or CC)+IUI	—	15/45 (33%)
Dodson 1991[169]	Male factor	Review	HMG+IUI	13/85 (15%)	13/39 (33%)
Martinez 1991[87]	Male factor	cross-over	HMG+IUI SP+IUI	2/28 (7%) 0/28	—
Evans 1991[170]	Semen factor	RCT, cross-over	CC+HMG (CC+HMG)+IUI (CC+HMG)+IPI	1/32 (3%) 0/22 3/38 (8%)	— — —

First author	Indications	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Martinez 1990[86]	Male factor	RCT, cross-over	CC+(IUI or TIC) SP+(IUI or TIC) (CC or sp)+IUI (CC or sp)+TIC	2/27 (7%) 2/26 (8%) 4/28 (14%) 0/25 —	— — —
Ho 1989[83]	Idiopathic male	RCT, 6 cycles, Sequential	IUI TIC	0/114 1/124 (0.8%)	— —
te Velde 1989[84]	Male factor	RCT, 6 cycles, sequential	IUI TIC	3/112 (27%) 2/90 (22%)	— —
Friedman 1989[82]	Male factor	RCT, 7 cycles, sequential	IUI ICI+TIC	2/45 (44%) 0/45	2/19 (11%) 0/19
Hughes 1987[81]	Oligoasthenospermia	RCT	IUI ICI TIC	0/32 0/31 4/45 (9%)	— — —
Cruz 1986[79]	Oligoasthenospermia	RCT, 6 cycles sequential	(CC+HMG or HMG)+IUI (CC+HMG or HMG)+ICI	7/96 (14%) 1/86 (2%)	— —
Kerin 1984[78]	Poor quality semen	RCT, 4 cycles, sequential	NI TIC IUI	1/34 (3%) 0/38 8/39 (20%)	— — —
Thomas 1986[80]	Abnormal semen analysis	CT, 3 cycles sequential	IUI TIC	0/30 0/30	— —
Aboulghar 1991[171]	Idiopathic male	RCT	Fresh semen IUI Best semen IUI	9/219(4%) 19/209 (9%)	9/77 (12%) 19/73 (26%)
Blumenfeld 1989[146]	Male factor	Report	(CC or HMG)+IUI	7/46 (15%)	—
Kirby 1991[85]	Moderate semen factor	RCT, 6 cycles, cross-over	IUI TIC	14/218 (6%) 8/177 (5%)	— —
	Severe semen factor		IUI TIC	10/179 (6%) 2/154 (1%)	— —
Horvath 1989[172]	Male factor	Review	(CC+HMG+HCG)+IUI	6/175 (3%)	—
Hovatta 1990[173]	Male factor	RCT	CC+(IUI or IPI)	—	5/34 (15%)
Friedman 1991[88]	Male factor	Review	IUI	18/276 (7%)	—
Melis 1987[174]	Male factor	RCT 6 cycles after failure:	ICI+TIC CC+(ICI+TIC) (CC+FSH)+(ICI+TIC)	— — —	5/42 (12%) 5/48 (10%) 7/10 (70%)
Byrd 1987[175]	Male factor Asthenospermia Asthenospermia & oligospermia Sperm antibodies Anatomic disorder	Review	IUI	5/9 (56%) 3/27 (11%) 0/17 1/4 (25%)	5/6 (83%) 3/9 (33%) 0/4 1/2 (50%)
Confino 1986[176]	Male factor	Review	IUI	0/108	0/27
Dmowski 1979[177]	Male factor	Review	IUI	4/90 (4%)	4/27 (15%)
Glass 1978[178]	Male factor	Review	IUI	0/67	0/19
Harris 1981[179]	Male factor	Review	IUI	3/120 (3%)	3/20 (15%)
Hull 1986[180]	Male factor	Review	IUI	0/11	0/4
Bolton 1989[181]	Male factor	Review	CC+IUI	5/158 (3%)	5/29 (17%)
Hewitt 1985[182]	Male factor	Review	CC+IUI IVF-ET	3/64 (5%) 16/75 (21%)	3/36 (8%) 15/50 (30%)
Sunde 1988[183]	Male factor	Review	(CC or HMG)+IUI	8/56 (14%)	8/40 (20%)
Glazener 1987[184]	Semen factor Sperm antibodies	RCT, 6 cycles cross-over	ICI Natural ICI Natural	1/100 (1%) 1/87 (1%) 0/114 0/105	1/18 (6%) 1/17 (6%) 0/19 0/19
Leeton 1987[21]	Male factor	RCT	GIFT IVF-ET	2/7 (28%) 2/7 (28%)	2/7 (28%) 2/7 (28%)
ILA 1991[45]	Male factor	Report	IVF (+donor semen) GIFT (+donor semen)	–/2567 (14%) –/1074 (19%)	— —
HFEA 1992[44]	Male factor	Report	IVF-ET (+donor semen)	–/2861 (16%)	—
MRI-SART-AFS 1991[53]	Male factor	Report	IVF or GIFT	342/2322 (15%)	—
Craft 1989[185]	Sperm abnormality	Review	GIFT (+donor semen)	141/419 (33%)	—
Jansen 1990[186]	Oligospermia	Review	GIFT	42/148 (28%)	—
Hull 1992[51]	Sperm dysfunction	Review	IVF-ET	21/141 (15%)	—
Tan 1992[52]	Male factor	Review	IVF-ET	—	55/196 (28%)

First author	Indications	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Borrero 1988[187]	Male factor	Review	GIFT	4/30 (13%)	—
Braeckmans 1987[188]	Male factor	Review	GIFT	2/16 (13%)	—
Wong 1988[189]	Oligospermia	Review	GIFT	3/18 (17%)	—
Okuyama 1988[77]	Varicocele	CT	Surgical repair		
			6 mon.	—	23/141 (16%)
			12 mon.	—	37/141 (26%)
			24 mon.	—	41/141 (29%)
			31 mon.	—	43/141 (30%)
			Uncorrected		
			6 mon.	—	6/83 (7%)
			12 mon.	—	11/83 (13%)
			29 mon.	—	15/83 (18%)
Mordel 1990[74]	Varicocele	Review	Spermatic vein ligation, 6–142 mon.		10/36 (28%)
Nilsson 1979[76]	Left-sided varicocele	RCT	Ligation (36–74 mon.?)	—	4/51 (8%)
			Control (36–74 mon.?)		8/45 (18%)

Table A–3 *Studies of the treatment of anovulatory subfertility*

Author	Indications	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Shepard 1979[190]	Anovulatory	Review	CC, 50–250 mg daily	47/163 (29%)	76%
Hammond 1983[191]	Anovulatory	Review	CC, (−/+HCG) 50–150 mg, daily	77/369 (21%)	48%
Drake 1978[192]	Anovulatory	Review	CC+HCG, 50–250 mg daily	33/179 (18%)	73%
Kase 1967[193]	Anovulatory+	Review	CC, 50–100 mg daily	21/346 (6%)	—
Wu 1989[194]	Anovulatory+	RCT	CC, 50–100 mg		
			day 2	6/92 (7%)	—
			day 3	4/105 (6%)	—
			day 4	9/132 (7%)	—
			day 5	8/85 (9%)	—
Hull 1979[114]	Amenorrhoea	Review	CC/BC/HMG +	—	55/59 (93%)
Connaughton 1974[195]	Anovulatory	RCT	Cisclomiphene, 5 mg	2/18 (11%)	—
			Cisclomiphene, 10 mg	8/40 (20%)	—
			Placebo	4/31 (13%)	—
Abdul-karim 1990[196]	Anovulatory (93% PCOS)	Review	CC	7/315 (2%)	—
			HMG	24/208 (12%)	
Filicori 1991[123]	Hypogonadotropic amenorrhoea	Review	Pulsatile GnRH		
	primary:			9/40 (23%)	9/30 (30%)
	other:			17/55 (31%)	17/33 (52%)
	PCOS			19/92 (21%)	19/51 (37%)
Braat 1991[116]	Amenorrhoea	Review	Pulsatile GnRH	55/272 (20%)	—
Traub 1987[197]	PCOS	Review	FSH	—	3/5 (60%)
Fleming 1988[121]	CC-resistant PCOS+	Review	(GnRH−a)+HMG+hCG	27/80 (34%)	27/35 (77%)
			HMG+hCG	19/120 (16%)	19/45 (42%)
McFaul 1990[119]	CC-resistant PCOS	RCT, cross-over	HMG	4/41 (10%)	4/15 (27%)
			FSH daily	6/68 (9%)	6/34 (18%)
			FSH alternative day	9/70 (13%)	9/34 (26%)
			FSH pulsatile	1/31 (3%)	1/16 (6%)
Larsen 1990[120]	CC-resistant PCOS	RCT, cross-over	HMG	1/15 (7%)	—
			FSH	1/15 (7%)	—
Seibel 1985[198]	CC-resistant PCOS	RCT	HMG+HCG	4/23 (17%)	4/13 (31%)
			uFSH	1/11 (9%)	1/10 (10%)
Rossmanith 1987[199]	CC-resistant PCOS	RCT	HMG-im	1/9 (11%)	1/5 (20%)
			HMG-pulsatile	1/9 (11%)	1/5 (20%)
McFaul 1989[200]	CC-resistant PCOS	RCT, cross-over	FSH, daily	3/20 (15%)	3/9 (33%)
			FSH alternative day	6/19 (32%)	6/9 (67%)
Remorgida 1991[201]	CC-resistant PCOS	RCT, cross-over	Pul−GnRH+FSH	3/8 (38%)	—
			FSH	1/7 (14%)	—

Author	Indications	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Sagle 1991[202]	CC-resistant PCOS	RCT	HMG FSH	5/40 (13%) 5/35 (14%)	5/15 (33%) 5/15 (33%)
Buvat 1989[203]	CC-resistant PCOS+	RCT, cross-over	FSH/conventional FSH/slow	2/21 (10%) 7/44 (16%)	2/17 (12%) 7/23 (30%)
Ory 1985[204]	CC-resistant PCOS+	Review	Pulsatile GnRH	0/6	0/4
Burger 1986[205]	CC-resistant PCOS	Review	Pulsatile GnRH	5/85 (6%)	5/11 (45%)
Hurwitz 1986[206]	CC-resistant PCOS	Review	Pulsatile GnRH	0/12	0/4
Wilson 1988[207]	CC-resistant PCOS	Review	Pulsatile GnRH	0/9	0/5
Surrey 1989[208]	CC-resistant PCOS	Review	Pulsatile GnRH	0/16	0/9
Homburg 1989[209]	CC-resistant Hypogonadotropic Hypogonadism: Amenorrhoea: Organic pituitary disease: PCOS:	Review	Pulsatile GnRH	 38/129 (29%) 21/60 (35%) 11/52 (21%) 30/193 (16%)	 38/39 (97%) 21/17 (23%) 11/15 (73%) 30/47 (64%)
Ross 1985[210]	CC-resistant anovulation	Review	Pulsatile GnRH	10/54 (19%)	10/18 (56%)
Tal 1985[118]	CC-resistant anovulation -oligoovulation:	RCT	CC+HMG HMG CC+HMG HMG	2/2 (100%) 3/9 (33%) 4/22 (18%) 5/19 (26%)	— — — —
Gadir 1992[211]	HMG-resistant PCOS	RCT	OE+HMG IN+LH−RH−a	7/68 (10%) 8/66 (12%)	7/16 (44%) 8/17 (47%)
Tredway 1990[168]	Ovulatory dysfunction	Review	(Sp or CC)+IUI	—	6/22 (27%)
Mio 1991[212]	OS-resistant PCOS or PCO	Review	USFA+OS	9/127 (7%)	9/18 (50%)

Table A–4. *Studies of the treatment of unexplained subfertility*

Author	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Fisch 1989[22]	RCT, 4 cycles	CC, 100 mg, daily CC/HCG Placebo/HCG placebo	7/136 (5%) 3/154 (2%) 4/130 (3%) 0/144 (0%)	7/37 (19%) 3/39 (8%) 4/39 (11%) 0/36
Glazener 1990[141]	RCT, 3 cycles, cross-over	CC, 100 mg, daily placebo	24/294 (8%) 15/295 (5%)	— —
Harrison 1983[213]	RCT, 6 cycles, cross-over	CC + HCG Placebo + HCG	5/159 (3%) 1/158 (0.6%)	5/30 (17%) 1/27 (4%)
Wright 1979[144]	RCT, 6 months	Bromocriptine Placebo	— —	7/24 (29%) 5/23 (22%)
McBain 1979[145]	RCT, 3 months cross-over	Bromocriptine Placebo	— —	4/25 (16%) 4/25 (16%)
Van Dijk 1979[142]	RCT, 6 months	Danazol Placebo	— —	5/21 (24%) 1/19 (5%)
Iffland 1989[143]	RCT, 3 months	Danazol Placebo	— —	0/11 (0%) 1/17 (6%)
Welner 1988+[214]	Review	HMG+HCG	12/388 (3%)	12/97 (12%)
Wang 1979[215]	Review	HMG	3/13 (23%)	3/6 (50%)
Forrler 1986[216]	Review	(CC/HMG)+IPI	—	3/10 (30%)
Daly 1989[20]	CT	HMG or HMG+IUI observation	6/55 (11%) — (3.5%)	6/20 (30%) —
Serhal 1988[217]	CT ?	IUI HMG HMG+IUI HMG+IUI+IPI	1/30 (3%) 3/49 (6%) 6/19 (32%) 3/15 (20%)	1/15 (7%) 3/25 (12%) 6/15 (40%) 3/7 (43%)
Dodson 1991[169]	Review	HMG+IUI	17/116 (15%)	17/57 (30%)
Blumenfeld 1989[146]	Report	(CC or HMG)+IUI	6/17 (35%)	6/8 (75%)
Sunde 1988[183]	Review	(CC or HMG)+IUI	1/15 (7%)	1/11 (9%)
Hewitt 1985[182]	Review	CC+IUI IVF-ET	1/12 (8%) 13/64 (20%)	1/9 (11%) 13/59 (22%)

Author	Design	Treatment	Pregnancy/cycle	Pregnancy/patient
Byrd 1987[175]	Review	IUI	6/48 (13%)	6/14 (43%)
Deaton 1990[147]	RCT, 4 cycles, cross-over	CC+HCG+IUI	7/72 (10%)	—
		TIC	5/150 (3%)	—
Friedman 1991[88]	Review	IUI	14/224 (6%)	14/59 (24%)
Kirby 1991[85]	RCT, 6 cycles, cross-over	IUI	6/145 (4%)	—
		TIC	3/123 (2%)	—
Melis 1987[174]	RCT, 6 cycles	ICI+VI	—	1/16 (6%)
		CC+(ICI+VI)	—	0/9 (0%)
	after failure:	(CC+FSH)+(ICI+VI)	—	4/7 (57%)
Hovatta 1990[173]	RCT	CC+(IUI or IPI)	—	22/61 (36%)
Martinez 1990[86]	RCT, cross-over	CC+(IUI or TIC)	3/36 (8%)	—
		SP+(IUI or TIC)	1/36 (3%)	—
		(CC or SP)+IUI	3/36 (8%)	—
		(CC or SP)+TIC	1/36 (3%)	—
Martinez 1991[87]	RCT ? cross-over	HMG+(HCG or LH)+IUI	4/46 (9%)	—
		HMG+(HCG or LH)+TIC	2/46 (4%)	—
Dickey 1991[218]	Review	HMG+IUI	15/83 (13%)	—
Karlstrom 1991[219]	CT	IPI	9/115 (8%)	
Evans 1991[170]	RCT, cross-over	(CC+HMG)+TIC	1/36 (3%)	—
		(CC+HMG)+IUI	2/27 (7%)	—
		(CC+HMG)+IPI	9/56 (16%)	—
Campos-Liete 1992[220]	RCT, cross-over	(CC or HMG)+IPI	0/14 (0%)	—
		(CC or HMG)+TIC	3/14 (21%)	—
Check 1989[221]	RCT, 8 months	CC-male partner	—	29/50 (58%)
		ascorbic acid	—	8/50 (16%)
Leeton 1987[21]	RCT, cross-over	IVF-ET	6/30 (20%)	6/30 (20%)
		GIFT	7/37 (19%)	7/45 (16%)
Murdoch 1991[148]	Cross-over	GIFT	14/99 (14%)	—
		SP	14/875 (2%)	—
Devroey 1989[149]	Review	ZIFT	23/61 (38%)	23/54 (43%)
Tredway 1990[168]	Review	(SP or OS)+IUI	—	0/2
ILA 1991[45]	Report	IVF-ET	282/1985 (14%)	—
		GIFT	296/1466 (20%)	—
HFEA 1992[44]	Report	IVF-ET	363/2372 (15%)	—
MRI 1991[53]	Report	IVF or GIFT	184/1042 (18%)	—
Craft 1989[185]	Review	GIFT (+ donor semen)	116/340 (34%)	—
Jansen 1990[186]	Review	GIFT	88/253 (35%)	—
Navot 1988[222]	Review	IVF-ET	22/67 (32%)	—
Audibert 1989[223]	Review	IVF-ET	30/217 (14%)	—
Crosignani 1991[224]	RCT ?	IVF-ET	25/86 (29%)	—
		GIFT	63/181 (35%)	—
		OS+IUI	55/241 (23%)	—
		OS+IPI	6/35 (17%)	—
		OS	9/105 (9%)	—
Braeckmans 1987[188]	Review	GIFT	11/39 (28%)	—
Borrero 1988[187]	Review	GIFT	22/52 (42%)	—
Wong 1988[189]	Review	GIFT	14/42 (33%)	—
Tan 1992[52]	Review	IVF-ET	—	414/744 (56%)

A database of randomised trials in subfertility has been created in the Institute of Epidemiology and Health Services Research (University of Leeds) under the direction of Professor Richard Lilford, in collaboration with Dr Ed Hughes and Professor John Collins of the McMaster University, Ontario. Trials are classified according to subject area, study design and quality criteria.

Further details are available from Dr Patrick Vandekerckhove at the above Institute.

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Bulletin 4 will discuss purchasing and providing issues related to the surgical management of glue ear.

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