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Economic implications of assisted reproductive techniques: a systematic review*

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BACKGROUND: Approximately one in six couples experiences problems with their fertility at some point in their reproductive lives. The economic implications of the use of assisted reproductive techniques require consideration. Herein, the health economics research in this area are critically appraised. METHODS: Multiple strategies were used to identify relevant studies. Each title and abstract was independently reviewed by two members of the study team and categorized according to perceived relevance. The selected papers were then assessed for quality and data were extracted, converted to UK pounds sterling at 1999/2000 prices, tabulated and critically appraised. RESULTS: A total of 2547 papers was identified through the searches; this resulted in 30 economic evaluations, 22 cost studies and five economic benefit studies that met the selection criteria. The quality of these studies was mixed; many failed to disaggregate costs, discount future costs or conduct sensitivity analyses. Consistent findings included the following: initiating treatment with intrauterine insemination appeared to be more cost-effective than IVF; vasectomy reversal appeared to be more cost-effective than ICSI; factors associated with poor prognosis decreased the cost-effectiveness of interventions. CONCLUSIONS: The cost-effectiveness of different interventions should be considered when making decisions about treatment. Future economic appraisals of assisted reproductive techniques would benefit from more robust methodology than is evident in much of the published literature to date.

Keywords: economics/infertility/systematic review

Introduction

It is estimated that approximately one in six couples experiences problems with their fertility at some point in their reproductive lives (Human Fertilisation and Embryology Authority, 2002). Moreover, the number of women experiencing infertility is expected to increase in the next 20 years due to women delaying childbearing. An increase in demand for infertility treatment is anticipated as a consequence (Stephen and Chandra, 1998).

Assisted reproductive technology (ART) covers a range of interventions [IVF, gamete intra-Fallopian transfer (GIFT) and ICSI], all of which have the ultimate aim of assisting the 'infertile' patient to become pregnant and deliver a live infant. Predominantly, ART involves the manipulation of gametes—both at a pharmacological level (i.e. ovarian stimulation) and at an in-vitro level, sometimes using micromanipulation (e.g. ICSI). Additionally, surgical interventions may be required to treat damaged pelvic organs.

The use of ART, though often perceived to be discretionary and expensive, has important economic implications. Debate abounds regarding both the allocation of finite resources in this area and the appropriate balance of costs borne by individual patients and society (Redmayne and Klein, 1993; Lieberman and Matson, 1995; Ledger and Skull, 2000). Different countries pursue different policies regarding which treatments, if any, are publicly funded. For example, in France, IVF is fully reimbursed by the social security system, whilst in Belgium, Denmark and Norway the state bears most, but not all, of the cost of IVF (Redmayne and Klein, 1993). In contrast, there are wide variations in local provision of ART via the National Health Service (NHS) in England and Wales—the so-called 'postcode lottery' effect, which results in inequalities in access to NHS-funded ART (Brown, 1999). According to recent estimates, only one in four IVF cycles performed in the UK is funded by the NHS (Ledger and Skull, 2000).

Economic appraisal provides a useful approach to informing current debate in this area. Economic studies fall into three broad categories: full economic evaluations; costing studies; and economic benefit studies (Table I). Economic evaluation

*The views expressed in this paper are those of the authors and do not necessarily reflect those of the Department of Health.

Table I. Summary of types of economic appraisal

Full economic evaluations
Economic studies that compare the costs and outcomes of two or more treatments. The three forms of economic evaluation differ in how they measure and value outcomes:
- Cost-effectiveness analysis: Outcomes are measured in natural or physical units such as confirmed pregnancy or baby delivered. Includes cost minimization analysis in which the outcomes are equal.
- Cost-utility analysis: A refinement of cost-effectiveness analysis, it constructs a single index of outcomes covering both mortality and morbidity. The most commonly used is the quality adjusted life year (QALY).
- Cost-benefit analysis: Costs and outcomes are both measured in monetary units. Estimates whether benefits of activities exceed their costs.

Costing study
A form of economic study in which the cost of one or more treatment options is estimated by 'top-down' methods involving disaggregating hospital, clinic or speciality expenditure, or 'bottom-up' methods by synthesizing resources used and the unit costs of these resources.

Economic benefit studies
A form of economic study in which patient preferences for health care interventions and their outcomes are valued using economic techniques such as contingent valuation (willingness to pay) or conjoint analysis.

has been defined as 'the comparative analysis of alternative courses of action in terms of both their costs and consequences' (Drummond *et al.*, 1997). Application of economic evaluation to ART may inform decision making at a variety of levels. At the national level, it may inform policy makers (such as the Department of Health and NHS); at the level of the individual clinic, it may inform clinicians or managers with budgetary responsibilities; and at the individual clinician and/or patient level, it may assist with the clinical decision-making process.

A few studies have dominated economic appraisal of ART to date (Neumann *et al*., 1994; Van Voorhis *et al*., 1998; Van Voorhis and Syrop, 2000), but these have not provided a systematic overview of the economic evidence. Herein, we present the results of the first systematic review of the economic implications of ART. The review focuses on studies conducted in developed countries that included an economic component, including studies of economic costs, economic benefits and, more specifically, the cost-effectiveness of different ARTs. This review had the exploratory objective of condensing and presenting in a readily understandable format the large amount of information contained in numerous published and unpublished sources. Unlike systematic reviews of the clinical evidence, the methods of systematically reviewing economic appraisals remain largely undeveloped. The health economics research in this area was critically appraised, the aim being to provide a stimulus for increasing methodological robustness in this area of health care.

Materials and methods

Literature search

Multiple strategies were used to identify relevant economic studies of ART. The following computerized databases were searched: Medline, CINAHL, EconLit, Science Citation Index (SCI), Social Science Citation Index, Index to Scientific and Technical Proceedings (ISTP), EMBASE, Cochrane Library (CDSR), York Database of Abstracts of Reviews of Effectiveness (DARE), NHS Economic Evaluation Database (NEED), and the Database of Consortium of University Research Libraries (COPAC). Additionally, formal searches of the ASLIB Index to British Theses and Current Research in Britain (CRIB) were conducted for Masters and PhD theses accepted by British universities. Books and pamphlets held in the National Perinatal Epidemiology Unit (NPEU) library relating to economic aspects of ART were hand searched. Published and unpublished manuscripts identified through fellow UK health economic researchers and other contacts were reviewed to determine their relevance to the study.

An initial search strategy was developed by the research team and tested extensively on Medline. The search terms (available from the authors) were then applied (with small modifications) to all electronic databases. The reference lists of all papers identified by the searches were reviewed to identify relevant additional studies. Studies were included in the literature search if they were published between January 1990 and December 2000; if they had been conducted in a developed country; if the paper was in English or French (for pragmatic reasons); and if the focus was human research. In order to keep apace of rapidly changing technology in the field of ART, an additional Medline search was conducted for the time period January 2001 to March 2001.

Categorization and assessment of studies

Each study was categorized independently by two of the investigating team on the basis of its title, medical subject heading (MeSH) and, where available, its abstract. The following initial criteria were used to determine the relevance of each study to the systematic review:

(A) The study reports research on the costs or utilization of ART and/or its sequelae and includes formal economic evaluation.
(B) The study reports economic aspects of ART and/or its sequelae, and contains useful primary or secondary cost or utilization data.
(C) The study reports benefits of ART and/or its sequelae using economic methods.
(D) The study may prove to have useful economic information but does not fall clearly into category (A), (B) or (C).
(E) The study discusses economic aspects of policies for ART and/or its sequelae, but not (A), (B) or (C) above.
(F) The study does not have any relevance to the economic aspects of ART.

Studies in categories (A), (B) and (C) were considered relevant to this systematic review and were obtained from local and national libraries. A decision was made to sample 20% of the studies categorized as (D). If 20% of this subset had been considered relevant to the aims of this review, then the remainder would have been

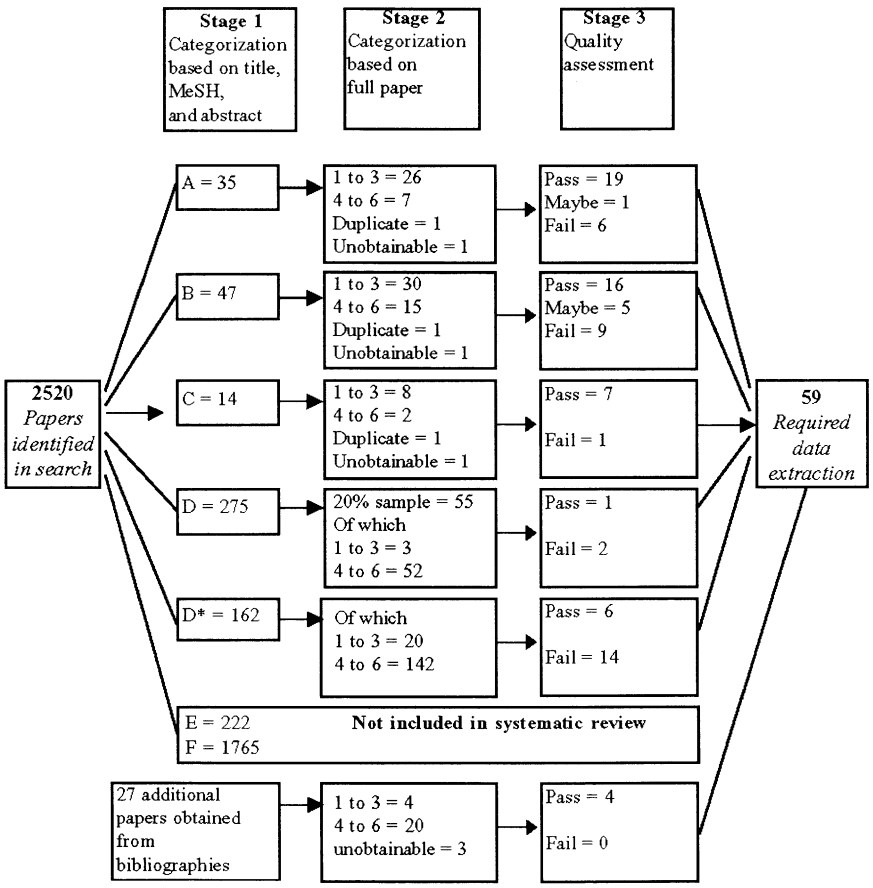

Figure 1. Flow chart of the numbers of papers at each stage of the review. A = study reports research on the costs or utilization of ART and/or its sequelae and includes formal economic evaluation; B = study reports economic aspects of ART and/or its sequelae, and contains useful primary or secondary cost or utilization data; C = study reports benefits of ART and/or its sequelae using economic methods; D = study may have useful economic information but does not obviously fall into category A, B or C; D* = D paper upgraded for further review; E = study discusses economic aspects of policies for ART and/or its sequelae, but not A, B or C above; F = study does not have any relevance to the economic aspects of ART. 1 = Economic evaluation (cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis); 2 = Other cost or resource utilization study; 3 = Economic benefit study (willingness to pay, conjoint analysis); 4 = Review of economic aspects of ART; 5 = Other, such as survey of resources and facilities or discussion of health finance and policy; 6 = Not relevant to economic aspects of ART.

obtained. One of the investigators (L.D.) upgraded any (D) paper to (D*) if it warranted additional review. All (D*) papers were obtained for secondary review; (E) and (F) papers were excluded from the review.

All retrieved studies were reviewed in full by two reviewers (one of whom was a health economist) and independently allocated to one of the following categories:

1. Economic evaluation (cost-minimization analysis, cost-effectiveness analysis, cost-utility analysis, cost-benefit analysis).
2. Other cost or resource utilization study.
3. Economic benefit study (willingness to pay, conjoint analysis).
4. Review of economic aspects of ART.
5. Other, such as survey of resources and facilities or discussion of health finance and policy.
6. Not relevant to economic aspects of ART.

At each stage, disagreements over the categorization of studies were resolved by consensus. All studies finally categorized as economic evaluations, cost studies, or economic benefit studies were included in the systematic review, i.e. studies finally classified as (A)1, (A)2, (A)3, (B)1, (B)2, (B)3, (C)1, (C)2 or (C)3. All other studies were excluded from further review.

The methodological robustness of the selected studies was assessed using guidelines developed by a group of leading health economists and published by the *British Medical Journal* (Drummond and Jefferson, 1996). The study design, data collection methods, and analysis and interpretation of results were independently assessed by at least two reviewers. This was done using the complete checklist of 35 items contained within these guidelines for any study categorized as an economic evaluation; an abbreviated checklist of 17 items for any study categorized as a cost study; and a four-item checklist (Olsen and Smith, 2001) for any study categorized as an economic benefit study (all checklists are available from the authors). In addition, all studies finally classified as either economic evaluations or cost studies were assessed using a subset of four criteria considered by the authors to be of critical importance. Disagreements as to whether the studies met the requirements of the guidelines were resolved by discussion.

All cost data contained within the economic evaluations and cost studies were converted into UK pounds sterling using Purchasing Power Parities supplied by the Organisation for Economic Co-operation and Development (OECD, 2002). Once converted to UK pounds, the cost data were inflated to 1999/2000 prices using the NHS Hospital and Community Health Services Pay and Prices Inflation Index. Substantial methodological variations between the studies prevented a pooling of economic data akin to meta-analyses performed in the clinical literature. Therefore, the results of the

Table II. Summary of studies included in review (at 1999/2000 prices): economic evaluations

Author(s) (year)/country of publication	No. of observations	Focus and methods of study	Costs	Effectiveness	Cost-effectiveness	Comments
Comparison between different populations						
Trad *et al.* (1995)/USA	182 couples, 308 cycles, 73 allocated to 1 of 3 prognostic groups.	Probability of successful IVF in 3 prognostic groups. Retrospective reivew of patient records.	1VF £5986.	Pregnancy rates per cycle: Good prognosis 30% Medium prognosis 23% Poor prognosis 11%	Cost per pregnancy: Good prognosis £17 102 Medium prognosis £25 439 Poor prognosis £31 923	Cost of IVF from Neumann 1994. Not clear why only 73 of 182 allocated to prognostic group.
Suchartwatnachai *et al.*, (2000)/ Thailand	407 women, 722 stimulated cycles.	CE* of IVF in women aged <38 compared to ⩾38 years. Retrospective cohort study.	IVF £677–1354	Clinical pregnancy rate per cycle: 21.6% <38 years, 13.9% ⩾38 years Delivery per initiated cycle: 15.9% <38 years, 7.6% ⩾38 years	Cost per delivery: £9749 <38 years £34 976 ⩾38 years	Excludes indirect and neonatal costs. Uses patient charges, not true costs
Natural cycle versus stimulated IVF						
Daya *et al.* (1995)/Canada	240 natural cycles; number of women not stated.	CE* of natural cycle IVF (patient population) versus stimulated IVF (from literature).	Stimulated IVF £4250 Natural cycle IVF £898	Live birth per cycle: Natural cycle 6.8% Stimulated 16.1%	Cost per live birth (excluding cost of complications): Natural cycle £13 203 Stimulated £26 396	Comparison with costs and success rates from literature. Complications and neonatal cost consequences not included in analysis.
Nargund *et al.* (2001)/UK	52 women, 181 cycles.	Natural cycle IVF based on prospective cohort compared with stimulated IVF from Tan *et al.* (1992).	Stimulated IVF £1786 Natural cycle IVF £413	Pregnancy rate per natural cycle 12.7%, delivery rate 8.8%. Pregnancy rate after four natural cycles 46%, delivery rate 32% versus 34% with stimulated IVF (Tan *et al.*, 1992).	Cost per pregnancy £2979 for natural cycle compared with a range of £7938–13 230 for severe to mild tubal factor IVF.	Selected favourable population. Comparison from Tan *et al.* (1992). Costs from Philips *et al.* (2000) were charges rather than costs.
Delayed IVF versus standard timing						
Goeree *et al.* (1992)/Canada	399 couples, 205 undergoing IVF, 194 awaiting IVF.	RCT of couples undergoing IVF versus those awaiting IVF but receiving other treatment.	Pre-treatment evaluation £521 IVF £2531 Stimulated IUI for idiopathic £608–1458	Pregnancy rate per month 'at risk': Early treatment 1.1% Delayed treatment 0.8% Live births per month 'at risk': Early 0.8% Delayed 0.4%	Cost minimization analysis, incremental cost of early versus delayed IVF £1823 from societal perspective.	Excludes neonatal costs. Very thorough analysis, but unusually low success rates for IVF. Early treatment had a mean wait of 8 months.
Shared oocyte IVF						
Peskin *et al.* (1996)/USA	23 shared oocyte cycles; number of women not stated.	CE* of shared oocytes IVF based on retrospective data compared with routine IVF from Goldfarb *et al.* (1996).	IVF £6880 Hospital costs for twins £1438, triplets £6951 neonatal costs per day £4173	15 births resulted from the 23 cycles (65%).	Cost per woman delivered £16 999 compared with £25 732 (Goldfarb *et al.*, 1996).	Small sample size. Donor women aged ⩽35 years with predominantly tubal factor. Hospitalization and neonatal costs from Goldfarb *et al.* (1996).
rFSH versus uFSH						
Mantovani *et al.* (1999)/Italy	Theoretical cohort of 10 000 patients with a 1-year time horizon.	Comparison of CE* of recombinant versus urinary FSH using Markov modelling.	Drug cost per cycle: rFSH £1346 uFSH £631	Pregnancy rates: rFSH 22.9% uFSH 17.9%	Cost per ongoing pregnancy: rFSH £13 302 uFSH £14 506	Based on costs split 80% private, 20% public. Costs are tariffs charged by private clinics.

Table II. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus and methods of study	Costs	Effectiveness	Cost-effectiveness	Comments
Sykes *et al.* (2000)/UK	585 women received rFSH, numbers receiving uFSH not stated.	Comparison of CE* of recombinant versus urinary FSH using Markov modelling.	Resource use data from Delphi panel, 20 UK IVF clinics generated 'cost' data.	Cumulative ongoing pregnancy rates after 3 IVF cycles: rFSH: 57% uFSH: 44%	Cost per ongoing pregnancy: rFSH £8992 uFSH £9472–10 834	Conference abstract only. Insufficient data to judge quality of study.
Van Loon *et al.* (2000)/Greece	Theoretical cohort.	Comparison of CE* of recombinant versus urinary FSH using Markov modelling.	IVF with rFSH £4368 IVF with uFSH £3750	Cumulative ongoing pregnancy rates after 3 IVF cycles: rFSH: fresh 51%, frozen 10% uFSH: fresh 44% frozen 4%	Cost per ongoing pregnancy: rFSH £7117 uFSH £7565	Sensitivity analysis showed that results were sensitive to costs of drugs and IVF.
IVF with cryopreservation of embryos						
Van Voorhis *et al.* (1995)/USA	610 women, 1000 oocyte retrievals Costs–334 initiated ART cycles.	IVF, GIFT and ZIFT cryopreservation compared with fresh embryo transfer. Retrospective review of patient records.	IVF £6364 GIFT £5277 ZIFT £7815 Cryopreservation £355 Embryo transfer £1247 Cryopreserved embryo cycle £1602	Fresh cycle deliveries per initiated cycles: IVF 18.2% (21/115) GIFT 27.3% (3/11) ZIFT 30.6% (34/111) Deliveries per oocyte retrieval 29.4% (fresh); pregnancy rate per retrieval increased by 6.6% by using cryopreserved embryos.	Cost per delivery: IVF £34 851 GIFT £19 347 ZIFT £25 514 Total fresh cycles £28 575 Cryopreserved ETs £8636	Excluded some obstetric and all neonatal complications, also indirect costs. Used patient charges, not costs. GIFT particularly small sample size.
IVF versus ovulation induction						
Fridstrom *et al.* (1999)/Sweden	28 infertile women with clomiphene-resistant polycystic ovary syndrome (PCOS). 15 women (41 cycles) had OI 13 women (30 cycles) had IVF.	Women referred to a university clinic prospectively randomized to OI or IVF.	IVF £1241 OI £753 Complications £687 Twin delivery £349 Triplets £364	Pregnancy rate per cycle: IVF 27% OI 10% Live birth rate per cycle: IVF 5/41 (12%) OI 9/30 (30%)	Cost per pregnancy: IVF £3816 OI £8625 Cost per maternity: IVF £5815 OI £9923	Small numbers. Included couples with tubal patency and normal sperm count. Patient costs not included, nor costs of neonatal care. Costs were lower when freeze–thawed embryos were used. Many of the women were overweight.
Karande *et al.* (1999)/USA	IVF group $n = 46$ Standard infertility treatment algorithm (SITA) $n = 50$	Outcome and CE* of IVF compared with a standard infertility treatment algorithm when used as first-line therapy for couples with infertility. RCT	IVF £9755 SITA £6812	Pregnancy rates: IVF 34% per embryo transfer SITA 24% per cycle	Cost per pregnancy: IVF £37 394 SITA £15 171	Small sample size. Excluded women aged >37 years, men with severe male factor. Complications not included. Used charges, not costs.
IVF versus IUI						
Peterson *et al.* (1994)/USA	47 hMG + IUI patients (99 cycles); 19 IVF patients (19 cycles); 21 patients receiving no treatment.	Comparison of effectiveness and CE* of 1–4 cycles of ovulation induction with hMG + IUI versus one cycles of IVF versus no treatment. Prospective, non-randomized, cohort study, follow-up for 1 year.	IVF £5529 per cycle hMG + IUI £1103 per cycle	Pregnancy rate: hMG + IUI 15% per cycle IVF 26% Take-home-baby rate: hMG + IUI 13% per cycle IVF 21% No treatment resulted in 14% pregnancy and live birth rate (1.4% per cycle).	Cost per pregnancy: hMG + IUI £7283 IVF £21 010	Small numbers. Excluded couples with significant male factor, endometriosis, bilateral non-patency of tubes and reversal of female sterilization. Used charges, not costs.

Table II. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus and methods of study	Costs	Effectiveness	Cost-effectiveness	Comments
Zayed *et al.* (1997)/UK	38 couples had stimulated IVF. 42 couples had stimulated IUI treatment.	CE* of SIUI treatment compared with SIVF in couples with unexplained and mild male factor infertility. Prospective trial.	SIVF £1005 per cycle SIUI £409 per cycle Embryo transfer £109	Live birth rates 18.4% per cycle SIVF 19.0% for SIUI	Cost per maternity SIUI £2096 SIVF £5026	Based on current costs in clinic, but year of prize data not stated. Costs simplistic; exclude patient costs. Patients not clearly randomized to treatment group (pseudorandomization). Sample size small.
Goverde *et al.* (2000)/Netherlands	86 couples IUI in spontaneous cycles; 85 stimulated IUI; 87 IVF.	Comparison of natural and stimulated IUI with IVF for couples with idiopathic or male subfertility. RCT.	IVF £1220 Natural cycle IUI £227 Stimulated IUI £339	Deliveries per started treatment: IVF 38% Natural cycle IUI 31% Stimulated IUI 37%	Costs per livebirth: IVF £9978 Natural IUI £3066 Stimulated IUI £3881	Detailed primary costing work. Excluded costs of infertility work-up, antenatal care and delivery. Also investigated effects of woman's age in Markov model.
Van Voorhis *et al.* (2001)/USA	1039 couples 3479 IUI cycles; 424 couples 551 IVF cycles.	Comparison of effectiveness and CE* of IUI versus IVF based on semen analysis results.	IUI £260–930 IVF £4953–8673	Pregnancy rate all cycles: $<10\times10^6$ sperm IUI 2% IVF 37% $>30\times10^6$ sperm IUI 10% IVF 43% Delivery rate all cycles: $<10\times10^6$ sperm IUI 1% IVF 32% $>30\times10^6$ sperm IUI 7% IVF 37%	Cost per delivery: $<10\times10^6$ sperm IUI £32 585 IVF £22 254 $>30\ 10^6$ sperm IUI £8296 IVF £18 644	Wide variation in cost estimates. Included costs of complications, but not obstetric or neonatal costs. With poor sperm count all IVF was with ICSI. IUI effectiveness data from secondary sources.
Female tubal factor infertility						
Khare *et al.* (1995)/USA	Theoretical model.	Theoretical pathways for diagnosis and treatment of hysterosalpinges and pelvic adhesions.	IVF £5612 Laparoscopy £2304–3367	From literature, pregnancy rates following Salpingostomy 28% Adhesiolysis 64% IVF 19%	Most efficient pathway was diagnosis and treatment adhesions at laparoscopy with no previous screening £14 128 per pregnancy.	Heroic assumptions about ongoing pregnancy. In common with other studies, uses charges not true costs.
Copperman *et al.* (1996)/USA	98 women; 67 underwent 92 cycles of IVF; 31 had tubal surgery.	CE* of IVF versus tubal surgery for women with tubal disease. Cohort study.	Pre-treatment evaluation £379 for IVF, £264 for surgery. IVF £4456 Surgery £3590 Complications £7644	Pregnancy rates: IVF 25% per cycle tubal surgery 19.3% in year following surgery	Including costs of complications, cost per pregnancy: IVF £18 131 Tubal surgery £18 601	Two quite different populations. Excludes patient costs. Used 'actual' costs rather than 'billed' costs.
Mol *et al.* (2001)/ Canada	2167 couples in the Canadian Infertility Treatment Evaluation Study database.	Decision analytic analysis comparing hysterosalpingography (HSG), laparoscopy, IVF and *Chlamydia* antibody testing.	HSG £56 Laparoscopy £547 IVF £5520 (Neumann *et al.*, 1994) Hospital costs: Singletons £6797 Twins £26 222 (Callahan *et al.*, 1994)	HSG and laparoscopy testing assumed to increase fertility prospects by 30%, treatment of endometriosis by 80%	Costs per additional live birth: HSG, then laparoscopy, then IVF £51 824. Immediate IVF £63 279	Secondary (unreliable) costs data for IVF and multiple births. Strongly dependent on female age.
Donor oocyte IVF						
Silva *et al.* (1998)/USA	22 women aged 40+ years, 24 GIFT cycles.	GIFT patient series. Comparison with SART data on donor oocyte IVF.	GIFT £4328 ± £609. Donor oocyte: £8625 (Legro *et al.*, 1997)	Delivery rates for women aged >40 years: GIFT 24% (6/24) Donor oocyte 37.5% (Legro *et al.*, 1997) Donor oocyte all ages 34.4% (SART, 1996)	Cost per delivery: GIFT: £17 311 ± £2435 Donor oocyte: £22 300 (Legro *et al.*, 1997) Donor oocyte: £17 562–21 953 (SART, 1996)	Small numbers; comparison with SART data and Legro *et al.* (1997) (a study which we reviewed but failed quality checklist).

Table II. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus and methods of study	Costs	Effectiveness	Cost-effectiveness	Comments
ICSI versus donor insemination						
Granberg *et al.* (1996)/Sweden	715 couples started 901 ICSI treatments, 608 couples underwent 1949 donor inseminations.	CE* of ICSI–IVF versus donor insemination (DI). Retrospective cohort study.	ICSI–IVF £3121 Donor insemination £582 Singleton delivery £839 Twins £1353 triplets £1950	Deliveries per started treatments: ICSI–IVF 24% DI 9% Deliveries per couple: ICSI–IVF 29% DI 28%	Cost per delivery: ICSI–IVF £13 218 DI £6719	Included costs associated with complications and multiple births. No sensitivity analysis. Effectiveness data from several clinics, but costs from only one.
ICSI versus surgical treatment of varicocele						
Schlegel (1997)/USA	710 cycles of IVF at four centres, 928 men who underwent varicocelectomy in 12 trials.	CE* of ICSI–IVF versus varicocelectomy based on four centres for IVF and secondary data from controlled trials. Modelling study.	Pre-treatment evaluation £267–382 ICSI–IVF £8473 Varicocelectomy £3007 Complications £1143–1871 Singleton delivery £7366 Twins £6951 Triplets £82 126	Pregnancy rates per cycle: ICSI–IVF 30% Varicocelectomy 33%	Cost per delivery: ICSI–IVF £46 585–66 658 Varicocelectomy £19 654	Included costs associated with time off work, complications and multiple births. Made assumptions about miscarriage rates and that three embryos are transferred. Excluded women aged >39 years. Not clear what length of follow-up after surgery.
ICSI versus vasectomy reversal						
Pavlovich and Schlegel (1997)/ USA	710 cycles of IVF at four centres, unstated numbers from five treatment series for microsurgical vasoepididymostomy and two series for microsurgical vasovasostomy.	CE* of treatments for vasectomy reversal: ICSI–IVF versus microsurgical vasoepididymostomy versus microsurgical vasovasostomy. Modelling study.	Pre-treatment evaluation £183 ICSI–IVF £15 224–21 003 Vasovasostomy £5074 Vasoepididymostomy £9765 Complications £40 Singleton delivery £3536	ICSI–IVF pregnancy rate 33%, delivery rate 30% Pregnancy rates: Vasovasostomy 53% Vasoepididymostomy 41% Overall vasectomy reversal PR 52%, delivery rate 47%	Cost per delivery: ICSI–IVF £54 260 Vasectomy reversal £19 060	Included costs associated with time off work, complications. Made assumptions about miscarriage rates. Excluded women aged >39 years. Not clear what length of follow-up after surgery.
Kolettis and Thomas (1997)/USA	55 men underwent 58 vasoepididymostomies, secondary data from four studies of ICSI–IVF.	Comparison of vasovasostomy versus microepidydymal sperm aspiration (MESA) ICSI–IVF. Retrospective cohort.	Vasoepididymostomy £6282 ICSI–IVF not stated Singleton delivery £4752 Twins £14 780 Triplets £147 804	Pregnancy rate 44% Delivery rate 29%	Cost per delivery: Vasoepididymostomy £17 449 MESA–ICSI–IVF £26 026	Included costs associated with time off work, complications and multiple births. Not clear whether excluded women aged >39 years. Median length of follow-up after surgery 19 months.
Donovan *et al.* (1998)/USA	27 men with unsuccessful vasectomy reversal.	Comparison of microepidydymal sperm aspiration (MESA) ICSI–IVF with repeat vasectomy reversal. Case series.	MESA–ICSI–IVF £11 998 Vasectomy reversal £5807	Pregnancy rate: MESA–ICSI–IVF 6/9 (67%) Vasectomy reversal 8/18 (44%)	Cost per pregnancy: MESA–ICSI–IVF £17 996 Vasectomy reversal £8711	Very small sample size. Costs are charges and exclude complications, subsequent maternity and neonatal care.
Deck and Berger (2000)/USA	42 men underwent vasectomy reversal, comparison with published literature.	Comparison of vasectomy reversal with ICSI-IVF in men with female partners aged >37 years.	ICSI–IVF £5629–8497 Vasectomy reversal £3285	Vasectomy reversal: 5 pregnancies and 4 live births of the 29 patients (17% and 14% respectively). ICSI–IVF in women aged >37 years 8% (Silber, *et al.*, 1997)	Cost per newborn: Vasectomy reversal £19 316 ICSI–IVF £70 372	Small sample size; 13 of the 42 lost to follow-up. Median follow-up of remaining 29 patients 25 months. Excluded costs of complications and multiple births.

Table II. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus and methods of study	Costs	Effectiveness	Cost-effectiveness	Comments
Multiple comparisons						
Van Voorhis *et al.* (1997)/USA	54 couples IUI 91 couples CC–IUI 52 couples hMG-IUI 136 ART 71 couples IVF–ET 24 couples Tubal surgery 26 couples Donor oocytes ART	CE* of various infertility treatments in a cohort of women treated at one academic institution in 1992 Retrospective cohort study.	Not stated	Delivery rate per cycle IUI 5.8% CC–IUI 6.3% hMG–IUI 17.5% ART 27.7% IVF–ET 22.2% Tubal surgery 12.5% Donor oocytes ART 32.3%	Cost per delivery: IUI £6839 Clomiphene IUI £6156 hMG IUI £8107 Tubal surgery £60 107 IVF–ET £34 013 DO ART £27 646 IVF/GIFT/ZIFT £29 196	Included costs of complications. Costs of diagnostic evaluation and obstetric care not included. Costs to patient and indirect costs of lost productivity not included. Used charges not costs. Also did analysis by female age and male sperm count.
Philips *et al.* (2000)/UK	Theoretical cohort.	CE* of treatment alternatives for five main causes of infertility. Modelling study.	Costs per couple: Pre-treatment evaluation £358 IVF £1786–5749 ICSI £2664–5278 Ovulatory disorders £524–2644 SIUI £1634–2148 DI for male factor £1672 SDIU for male factor £2148	Baseline pregnancy rate per cycle: IVF 15–26% SIUI 15–20% ICSI 31% Surgery: tubal 10–46% Endometriosis 5–31%	Cost per pregnancy: IVF £8712–20 268 Hyperprolactinaemia £594–668 PCOS £1545–2036 Non-PCOS £2014–3039 SIUI £3828–5308 Tubal surgery £2065–16 870 Endometriosis surgery: £2489–36,080 Vasectomy reversal £8604 DI for male factor £6203 SDIUI male factor £4536	Unit costs were extra contractual referral tariffs. Costs of complications and multiple births not included. Much of the analysis based on assumption.
Multiple pregnancies						
Wolner-Hanssen *et al.* (1998)/Sweden	1488 transferred embryos.	Comparison of costs per pregnancy after transfer of one or two embryos. Retrospective cohort.	*Singletons*: Hospital costs £291 Delivery £968 Per day in NICU £601 *Twins*: Hospital costs £1748 Delivery £1696 Per NICU day £10 485	Clinical implantation rate: 2 embryos transferred 25% 1 embryo, assumption varied between 10–30%	Cost per pregnancy: 2 embryos £9826 1 embryo, £125 771 (10%) or £110 974 (30%)	Single embryo transfer not widely practised, therefore success rates not known. Included costs from lost productivity.
WTP for IVF compared to actual charges						
Granberg *et al.* (1995)/Sweden	765 couples, 1079 cycles. WTP asked of 47 couples.	WTP for IVF compared to actual charges.	IVF £3048 (£3804 per started cycle Singleton delivery £839 Twins £1353 Triplets £1949	Deliveries per started treatment 34% Per embryo transfer (incl. Frozen–thawed) 27%	Range of WTP £0–30 000 but 55% <£12 000. Average cost per delivery was £11 300.	Most were already paying for treatment. Excluded neonatal and indirect costs.

*CE = cost effectiveness.
NICU = Neonatal intensive care unit.

studies are presented and discussed in a qualitative manner for each area of ART.

Results

Numbers of papers at different stages of review

A flowchart showing the total numbers of papers at different stages of the review is shown in Figure 1. A total of 2547 papers was identified by the literature searches, including 27 from bibliographies.

Of the 275 papers classified as (D), of uncertain value, a 20% random sample (55 papers) was examined in full. Of these papers, only three were considered relevant and the 20% threshold was not reached.

In the final review there were 30 studies that were finally classified as economic evaluations, 22 as cost studies and five as economic benefit studies (reported in seven papers). Further details of the stages of the review are shown in Figure 1.

Methodological limitations of included studies

A number of methodological issues were identified by the guidelines used to assess each economic study (Drummond and Jefferson, 1996). A key limitation of the economic evaluations and cost studies was the failure to provide detailed and disaggregated information on reported costs. Additionally, 19 of the 30 full economic evaluations (Goeree *et al.*, 1992; Peterson *et al.*, 1994; Daya *et al.*, 1995; Granberg *et al.*, 1995; Khare *et al.*, 1995; Trad *et al.*, 1995; Van Voorhis *et al.*, 1995, 1997, 2001; Goldfarb *et al.*, 1996; Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Schlegel, 1997; Donovan *et al.*, 1998; Silva *et al.*, 1998; Fridstrom *et al.*, 1999; Karande *et al.*, 1999; Mantovani *et al.*, 1999; Deck and Berger, 2000) and 12 of the 22 costing studies (Callahan *et al.*, 1993; Dewire *et al.*, 1994; Neumann *et al.*, 1994; Collins *et al.*, 1995, 1997; Rabin *et al.*, 1996; Hidlebaugh and O'Mara, 1997; Ficarra *et al.*, 1998; Ezeh *et al.*, 1999; Stovall *et al.*, 1999; Strawn *et al.*, 2000; Blackwell *et al.*, 2001) cite charges or a combination of costs and charges for ART services rather than actual costs. The remaining studies used alternative approaches based on cost accounting methods, incorporating detailed information about individual patient resource utilization or by allocating total costs by organizational workload. Finally, four of the 59 studies used primary cost data (Liao *et al.*, 1997; Zayed *et al.*, 1997; Goverde *et al.*, 2000; Suchartwatnachai *et al.*, 2000), while four used a combination of primary and secondary cost data (Goeree *et al.*, 1992; Peskin *et al.*, 1996; Rabin *et al.*, 1996; Granberg *et al.*, 1998).

The majority of studies had a short-term perspective, and long-term costs and benefits were not collected. Discounting was therefore not necessary. This is a process used by economists to weight current resources more highly than future resources. However, only one of the 18 full economic evaluations (Mol *et al.*, 2001) and none of the six cost studies that included costs associated with future care discounted future costs. The failure to discount future costs results in an overestimation of the costs that may accrue as a result of ART interventions. The results of these studies must therefore be viewed with a measure of caution.

Sensitivity analysis is an approach used by health economists to explore the robustness of an economic appraisal and investigate the effects of uncertainty (Briggs *et al.*, 1994). It was applied in 11 of 30 economic evaluations with varying degrees of completeness (Neumann *et al.*, 1994; Rabin *et al.*, 1996; Schlegel, 1997; Wolner-Hanssen and Rydhstroem, 1998; Mantovani *et al.*, 1999; Philips *et al.*, 2000; Suchartwatnachai *et al.*, 2000; Sykes *et al.*, 2000; Van Loon *et al.*, 2000; Mol *et al.*, 2001; Van Voorhis *et al.*, 2001). Nine of the studies stated the choice of variables used in the sensitivity analysis (Schlegel, 1997; Wolner-Hanssen and Rydhstroem, 1998; Mantovani *et al.*, 1999; Philips *et al.*, 2000; Suchartwatnachai *et al.*, 2000; Sykes *et al.*, 2000; Van Loon *et al.*, 2000; Mol *et al.*, 2001; Van Voorhis *et al.*, 2001), while three explicitly stated the type of sensitivity analysis performed (Mantovani *et al.*, 1999; Sykes *et al.*, 2000; Van Loon *et al.*, 2000).

The full economic evaluations included in the review met an average of 60% (range 39–89%) of applicable items on the *British Medical Journal* checklist used to assess methodological robustness. The included cost studies met an average of 56.3% (range 25–78%) of applicable items on the abbreviated checklist. There was no evidence that the methodological robustness of either the economic evaluations or cost studies varied by date of publication. The subsequent discussion of the study results should only be considered in light of the above methodological issues.

Results of reported studies

The results of the 57 studies included in the review are summarized in three tables according to method: economic evaluation (Table II), costing (Table III) and economic benefit studies (Table IV).

IVF

Costs of IVF and related procedures: Costs for IVF and related procedures are shown in Tables II and III. They were almost exclusively clinic charges to patients and thus do not accurately reflect real costs. The great variability in costs is largely explained by the definition of 'cost' adopted by the researchers as well as variations in the relative prices of resource inputs. Some studies included costs associated with complications (e.g. Pavlovich and Schlegel, 1997; Schlegel, 1997; Van Voorhis *et al*., 2001). Some costs and success rates were reported per 'started cycle', therefore including cancellations (e.g. Collins *et al.*, 1995; Daya *et al.*, 1995; Granberg *et al.*, 1998). Three of the studies (Trad *et al.*, 1995; Griffin and Panak, 1998; Mol *et al*., 2001) incorporated Neumann *et al.*'s 1994 baseline figure of $8000 (£6308) per IVF cycle, based on charges from six US facilities. Five additional studies cited costs associated with complications or loss of work based on Neumann *et al.*'s study (Copperman *et al.*, 1996; Goldfarb *et al.*, 1996; Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Schlegel, 1997).

Cost-effectiveness of IVF

Comparison between different populations: Two studies compared IVF treatment costs between clinically diverse patient populations (Trad *et al.*, 1995; Suchartwatnachai *et al.*, 2000). Trad *et al*., using costs from Neumann *et al.* (1994), estimated

Table III. Summary of types of economic appraisal: costing studies

Author(s) (year)/country of publication	No. of observations	Focus of study	Description of study	Costs	Comments
General costs					
Ryan (1996)/UK	No observation	Cost of drug therapy, tubal surgery, IVF and artificial insemination.	Costs were charges from unstated number of providers and charges to purchasers.	Amenorrhoea £3876 Oligomenorrhoea £9605 Endometriosis £4803 Tubal surgery £17 656 IVF £25 415 Artificial insemination £6757	Many assumptions about lengths of stay, duration of surgery, admissions to NICU. Included maternal and neonatal costs and complications.
Collins *et al.* (1997)/Canada	Hypothetical cohorts.	Cost of infertility diagnosis and treatment.	Modelling study based on prevalence of infertility, volume, distribution and costs of services and effectiveness of treatment.	Cost per live birth: IVF £25 499 per cycle IUI (male factor) £4563 IUI (idipoathic) £2457 Clomiphene £422–£1190 hMG £6991–£8277 Endometriosis surgery £10 021–11 930 Tubal surgery £11 930	Excluded costs of complications, obstetric and neonatal care. Cost 'guestimates'.
Costs of IVF					
Robinson *et al.* (1992)/UK	56 women, 27 used home LH monitor for 111 cycles, 29 had 123 DI cycles in routine manner.	Home urinary LH monitoring for donor insemination (DI).	Randomized prospective study.	Home monitoring kits £2.14 per assay, 2.2 assays required per cycle.	Not much detailed information on costs although reduced clinic visits mentioned.
Neumann *et al.* (1994)/USA	General population of couples undergoing IVF and two subgroups.	Costs of a successful delivery with IVF.	Modelling study based on listing of charges from six large IVF facilities and assumptions about complication and multiple birth costs. Probability of delivery based on literature.	Cost per live birth: First cycle IVF £52 566 Sixth cycle IVF £90 112 Sensitivity analysis range £34 693–167 110 Tubal disease range £39 424–57 344 Older women/male factor infertility range £126 157–630 784	IVF cycle costs based on charges. Includes estimates for NICU, maternal complications and loss of working days.
Gissler *et al.* (1995)/Finland	1015 IVF births, 190 697 other births.	Comparison of perinatal health and resource use of IVF births and other births.	Using the Finnish Medical Birth Registry examined characteristics and outcomes of IVF and non-IVF pregnancies and births.	IVF £1150 Cost per IVF birth £10 372 Cost per non-ART birth £1920	Costs per birth included obstetric and neonatal care. Not clear if costs or charges.
Stern *et al.* (1995)/Israel	Cost calculation based on 500 cycles/year in an IVF unit at Hadassah University Hospital.	Cost analysis of IVF in Israel.	Annual expenditures of an IVF unit in Israel; based on a theoretical cohort of 500 cycles. Calculated IVF cycle cost and cost of "take-home baby". Included direct and indirect medical costs.	Total cost of an IVF cycle: £1915 Total cost of a "take-home baby": £14 401	Analysis included maternal complication and multiple birth costs, as well as loss of working days. Based on hospital costs, not charges.
Goldfarb *et al.* (1996)/USA	413 stimulation cycles	Factors contributing to cost of IVF.	Review of IVF patients charges including antenatal, intrapartum and neonatal costs, also indirect costs. Cost associated with multiples had major effect on costs.	Stimulated IVF £5914 per oocyte retrieval Cost/woman for preterm labour: Singleton delivery £166 Twins £1483 Triplets £7170 Medical IVF cost/woman: £59 139 Ongoing neonatal care/loss work time: £14 545	Used patient charges not costs. Estimated added cost/woman delivered was nearly 9 times greater with triplets and quadruplets as compared to singletons and twins. Included costs of complications, obstetrics and neonatal costs.

Table III. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus of study	Description of study	Costs	Comments
Strawn *et al.* (2000)/USA	103 initiated cycles of fresh IVF in patients aged <41 years.	Costs of minimal precycle and ongoing cycle monitoring protocol for IVF.	Retrospective review. Costs were institutional charges. Determined cost savings for couples.	Direct cost of cycle monitoring for IVF was reduced by £367, without decreasing efficacy of procedure.	Cost reduction primarily due to fewer ultrasounds and estradiol assays. Authors state indirect costs are also reduced, but no data are provided.
Male surgical treatment					
Dewire *et al.* (1994)/USA	45 men underwent ligation, 36 men embolization.	Comparison of percutaneous embolization and surgical ligation. Follow-up for 1 year.	Patient series. Sperm density and motility were significantly better after treatment. There was no significant differences between the two groups.	Varicoelectomy £2977–4875 Embolizatiion £2914–4897	Patients selected their treatments. Cost analysis only on 9 patients.
Ficarra *et al.* (1998)/Italy	Not. stated.	Percutaneous, laparoscopic and surgical treatment of varicocele.	Detailed primary costing study.	Bilateral varicocelectomy £469 Surgical ligation £469 Sclerotherapy £91 Laparoscopic ligation £1023	The number of observations for costing study was not stated.
Ezeh *et al.* (1999)/UK	19 men underwent testicular biopsy under general anaesthesia, 21 with local analgesia.	Outpatient analgesia versus general anaesthesia for testicular sperm extraction in men with azoospermia.	Procedural and staffing costs from local finance department. Charges used to equate costs in private and NHS centres. Costs included consultations, procedural and overhead costs.	General anaesthesia £612 OP analgesia £250	Reduction in costs due to staffing, consumables and overheads.
Multiple births					
Callahan *et al.* (1993)/USA	13 208 women; 12 000 singleton, 1115 twin, 93 triplets + maternities.	Bed days used by mothers and neonates associated with multiple births.	Hospital costs at a large high risk obstetric centre in 1986–91.	Singleton delivery £2654 Twins £4544 Triplets + £96669	Only abstract, no details of costing.
Liao *et al.* (1997)/UK	92 women in 1990, 93 women in 1993.	Neonatal costs associated with reducing number of embryos transferred from three to two following IVF.	Clinical audit of change in embryo transfer. Resulted in considerable reduction in costs.	Cost per neonatal day: ITU £662 SCBU £282	Cost related solely to length of stay in NICU.
Miller *et al.* (2000)/USA	438 pregnancies.	Multifetal pregnancy reduction.	Retrospective review of patient records. Women who had their pregnancies reduced were compared to obstetric population. Averted costs considerable.	Fetal reduction £2173 Delivery costs from Callahan *et al.* (1994)	Only included survivors. No information on demographics of population.
Insurance/financing ARTs					
Collins *et al.* (1995)/USA	260 IVF centres active in the US in 1993.	Cost analysis of adding IVF treatment to a standard health care benefits package.	IVF utilization and outcomes for 1993 were estimated from data in an existing registry. IVF charges were determined from a 1993 survey of IVF clinics, and projected to 1995.	Average IVF charge: £4765 Total US expenditure for IVF services: £151.12 million Projected costs of adding IVF services to employer health plan in 1995: £1.98/year.	Analysis based on charges. IVF cost based on average charge for a single IVF treatment cycle. Excluded costs due to complications or multiple births.
Rabin *et al.* (1996)/USA	Theoretical model based on managed-care population.	Break-even capitation rates to provide fertility treatment under managed care.	Three standard treatment algorithms compared. Baseline assumptions from literature and experience.	Average costs of pregnancy/ year: £5016–15 757 depending on pregnancy rates, cost and utilization.	Makes numerous assumptions. Used a mixture of patient charges and costs.

Table III. *Continued*

Author(s) (year)/country of publication	No. of observations	Focus of study	Description of study	Costs	Comments
Hidlebaugh and O'Mara (1997)/USA	148 patients undergoing ART, 375 ART cycles.	Health maintenance organization perspective on costs of ART.	Cost analysis of clinic charges for IVF, GIFT, ZIFT, cryopreserved embryo transfer and donor oocyte.	ART cycle £3618 Singleton delivery £6894 Twins £15 015 Triplets £113 318 ART cycle cost per member £1.84.	Aggregated across all methods of ART. Charges not costs.
Griffin and Panak (1998)/ USA	Eight large health maintenance organizations + indemnity plan.	Cost of infertility-related services.	Diagnostic codes relevant to infertility management were examined and combined with charges from indemnity plan across years 1986–93.	IVF/GIFT £6115 ZIFT £7644 Cryopreservation £1529	Cites Neumann *et al*. (1994) for costs. Makes assumptions about proportion of specific treatments related to infertility.
Granberg *et al*. (1998)/ Sweden, Denmark, Norway, Finland, Iceland	15 392 cycles.	Financing of IVF in public and private care systems.	Mean costs of each procedure calculated for each country.	Stimulated IVF £1392–2900 Singleton delivery £696–1160 Twins £1044–2320 Triplets £1392–2900	Charges from clinics, not true costs. Excluded costs of multiple births.
Stovall *et al*. (1999)/USA	Healthcare policy members from January 1993 to December 1995.	Per member per month costs of infertility coverage in a university-based, self-insured, fee-for-service healthcare plan.	Historical prospective analysis. Healthcare costs were calculated from the ICD-9 codes, and included general and infertility-specific costs.	Total healthcare costs: £58 527 157 Infertility-specific costs: £461 011 Infertility accounted for 0.79% of total university healthcare costs. Mean total and infertility-specific PMPM healthcare costs were £58.33 and £0.45.	Payments made by a third party administrator were used to estimate the direct medical costs. Neither indirect not intangible costs were included. Costs of complications and multiple births were excluded.
Blackwell (2000)/USA	Claims experience of 27 811 members.	Hidden costs of infertility insurance.	Estimation of costs of treatments for infertility provided under other diagnoses.	Cost of infertility related claims per member per month £0.18–0.33.	Makes assumptions about proportion of treatments for diagnosis associated with infertility.
Blackwell *et al*. (2001)/USA	5046 women generated 39 new and 198 return visits.	Capitated health plan for infertility.	One-year retrospective study. All billing records reviewed to cost infertility services provided. Services provided according to a treatment algorithm.	IVF £2097	Aggregated across all methods of ART. Charges, not costs. Did not include neonatal costs.

Table IV. Summary of types of economic appraisal: economic benefit studies

Author(s) (year)/ Country of publication	No. of observations	Focus of study	Description of study	Findings	Comments
Neumann *et al.* (1994)/USA	389 surveys distributed to six sample groups (administrators, doctors, nurses, economists, and parents); response rate of 59%	WTP for IVF using contingent valuation (sampled nurses, MDs, parents, administrative staff, economics students).	Questionnaire asked if individuals would pay stated amounts for IVF, under various assumptions about the probability of success. Survey explored ex post and ex ante perspective, WTP for a public IVF programme, and how respondents value IVF relative to mortality risk reduction.	WTP (potential childbearers): £13 980 for a 10% chance of successful IVF in the event of infertility. Ex post WTP/ statistical baby—£140 137. Ex ante — £1.4 million.	59% response rate. Survey assumed IVF will produce healthy outcomes. Respondent knowledge of IVF not accounted for in analysis.
Ryan (1994, 1996)/Australia	700 questionnaires mailed to women attending an infertility service, 42% response rate.	Using WTP to assess other (dis)benefits of ART.	Questionnaire asked about attitudes of staff, location of clinic, continuity of contact, time on waiting list, speed of investigation, success rates and WTP.	Mean WTP was £1352. People on higher incomes were willing to pay more. Also successful treatment increases WTP.	42% response rate, but no reminders were sent.
Ryan (1995, 1999)/UK	414 questionnaires mailed to women attending assisted reproductive unit, 80% response rate.	Using conjoint analysis to determine importance of various factors in IVF.	Questionnaires asked about attitudes of staff, continuity of contact, time on waiting list, cost, follow-up support and success rates.	Attitudes of staff were more important than a 5% increase in success rates; continuity of care and follow-up support were less important.	Conjoint analysis only allows crude breakdown, e.g. attitudes of staff are 'good' or 'bad'.
Ryan (1997)/UK	1048 women mailed who had received IVF, 57% response rate. Two reminders sent.	WTP for IVF among women in receipt of IVF.	Questionnaires asked about attitudes of staff, location of clinic, continuity of contact, time on waiting list, speed of investigation, follow-up support, provision of information and counselling, success rates and WTP.	Mean WTP was £5450. WTP correlated with expected and actual success. Disappointment inversely correlated to WTP.	57% response rate. As with conjoint analysis, only crude measures ('good'/'bad' attitudes) in analysis.
Ryan (1998)/UK	1048 women mailed who had received IVF, 57% response rate. Two reminders sent.	Valuing psychological outcomes using WTP.	Questionnaire asked about psychological outcomes using the Satisfaction with Life Scale and the Positive Affect Negative Effect Scale.	Mean WTP was £6945. Mean psychological scores were significantly better where women had left the service with a child. Overall there were more benefits than disbenefits.	57% response rate. Same study as above. Respondent overload may have been a problem.

the cost of a successful pregnancy for women aged <33 years with no male-factor infertility at £17 102, compared with £31 923 in women aged >40 years. Suchartwatnachai *et al.* (2000) excluded indirect and neonatal costs but nevertheless came to the same conclusion, that the estimated cost per delivery in women aged ⩾38 years ~3.6 times higher than for women <38 years (see Table II).

Natural versus stimulated IVF cycles: Improvements in oocyte culture technique, sperm preparation, oocyte retrieval method, and ovarian stimulation regimens have increased pregnancy rates resulting from IVF (CDC, 1998, 1999, 2000, 2001; HFEA, 2001). However, because ovarian stimulation is expensive and not without risk, economic evaluations have been conducted to re-evaluate natural versus stimulated cycle IVF. Daya *et al.* (1995) acknowledged the relatively low success rates of natural cycle IVF (4.6% pregnancy rate and 3.8% live birth rate per cycle). However, the lower costs used in their analysis make natural cycle IVF more cost-effective than stimulated cycles with costs per live birth of ~£13 000 and £26 000 respectively (see Table II). Nargund *et al.* (2001) also concluded, from a selected favourable population, that natural cycles offer a cost-effective alternative to stimulated cycles, calculating natural cycle IVF costs to be ~23% of the cost of a stimulated cycle. Nargund *et al.* (2001) reported higher success rates than Daya *et al.* (1995) of 12.7% pregnancy per cycle and 8.8% live birth per cycle. Both these studies compared their own clinical data with data from the early 1990s that related to different populations and may have also included other costs. For example, it is not clear whether staff costs (including 'out of hours costs') and laboratory costs were included in costs of natural cycle IVF.

The lack of control over spontaneous ovulation during natural cycle IVF results in a greater intensity of ultrasonic and endocrine monitoring. A significant proportion of this may occur outside normal working hours, potentially resulting in higher staff costs. Add to this the cost of additional time off work for the couple undergoing multiple natural cycles (due to the significantly lower success rate) compared with stimulated cycles, and the economic benefits of natural cycle IVF may well be lost.

IVF with cryopreservation of embryos: Van Voorhis *et al.* (1995) evaluated the efficacy and cost-effectiveness of embryo cryopreservation compared with other assisted reproductive techniques (Van Voorhis *et al.,* 1995). In a retrospective review of 1000 oocyte retrievals at the University of Iowa in 1992, these authors found that the transfer of cryopreserved embryos increased the ongoing pregnancy rate per oocyte retrieval by 6.6%, and was cost-effective compared with other ARTs. The cost per delivery for cryopreserved ETs was between 25% and 45% that of fresh cycles. It should be noted, however, that some obstetric and all neonatal costs were excluded.

Other IVF considerations: Various other studies have examined the effects of delayed IVF treatment versus standard timing (Goeree *et al*., 1992), minimal precycle testing and ongoing monitoring (Strawn *et al*., 2000), shared oocytes (Peskin *et al*., 1996) and recombinant versus urinary FSH (Mantovani *et al*., 1999; Sykes *et al*., 2000; van Loon *et al*., 2000). These are included in Table II but, for brevity, are not discussed here.

Cost-effectiveness of IVF versus other ART techniques

IVF versus ovulation induction: Karande *et al.* (1999) conducted a prospective, randomized controlled trial comparing the outcome and cost of a traditional treatment algorithm (ovarian stimulation with clomiphene citrate and gonadotrophins followed by IVF) with IVF as the primary treatment for women with newly diagnosed infertility (Karande *et al.,* 1999). For the group undergoing standard infertility treatment, pregnancy rates were found to be higher, and costs per couple were not statistically different. Whereas cost differences between the groups diminished over time, pregnancy rates remained the same. Costs were based on charges and did not include the costs associated with maternity or neonatal care. Moreover, a higher proportion of women dropped out of the early IVF group compared with the standard treatment group (41 versus 28%) and the final numbers were small (27 and 36 women respectively).

For women with clomiphene-resistant polycystic ovarian syndrome (PCOS), Fridstrom *et al.* (1999) compared treatment outcome and costs of ovulation induction cycles with those of IVF. More pregnancies per completed cycle were noted in the IVF group than in the ovulation induction group. The cost per pregnancy resulting from ovulation induction was about twice that of the IVF group. The cost per term pregnancy including delivery was 1.6 times higher in the ovulation induction group, indicating that for this group of women with clomiphene-resistant PCOS, IVF was a cost-effective treatment. The number of women in this study was small, and neonatal costs were not included.

IVF versus intrauterine insemination (IUI): A number of economic evaluations has been performed which focuses on the cost-effectiveness of IVF when compared with IUI (Peterson *et al.*, 1994; Zayed *et al.*, 1997; Goverde *et al.*, 2000; Van Voorhis *et al.*, 2001). While population groups differed, all four studies demonstrated the cost-effectiveness of both stimulated and unstimulated IUI when compared with IVF (see Table II). For example, Peterson *et al.* (1994) conducted a cost-effectiveness analysis with a three-way comparison: IVF versus hMG + IUI versus no therapy. These authors found that one to four cycles of hMG + IUI was just as effective as one cycle of IVF in achieving pregnancy, and IVF was more expensive. Both IVF and hMG + IUI were more effective than no therapy. Again, small numbers and a selected favourable population require a cautious interpretation.

IVF versus tubal surgery in women: Three studies (Khare *et al.*, 1995; Copperman *et al.*, 1996; Mol *et al.*, 2001) compared the costs of IVF with other treatments when a diagnosis of tubal infertility was present. Khare *et al.* (1995) modelled the cost-effectiveness of six clinical pathways in the diagnosis and treatment of tubal factor infertility resulting from hydrosalpinges and pelvic adhesions. The authors found that the most cost-effective approach (£14 128 per pregnancy) was diagnosis and treatment of adhesions at laparoscopy with no previous screening. The most cost-effective approach for blocked tubes (£19 913 per pregnancy) was to begin with a

hysterosalpingogram (HSG). All pathways for adhesions and any screening pathway using HSG for hydrosalpinges were more cost-effective than IVF.

Mol *et al.* (2001) modelled 13 separate pathways to compare costs and effectiveness of various strategies in the work-up of subfertile couples suspected of having tubal pathology. The most cost-effective strategies used chlamydia antibody testing or HSG to decide when laparoscopy should be performed, either immediately or postponed for 1 year if the woman was still not pregnant. The authors suggested that the diagnostic work-up to detect tubal pathology in subfertile couples should start with chlamydia antibody testing in couples with relatively good fertility prospects, and immediate HSG in couples with relatively poor fertility prospects.

Copperman *et al.* (1996) conducted a primary costing study of two treatment modalities for infertility caused by tubal disease under two reimbursement models (Copperman *et al.,* 1996). These authors demonstrated success rates (defined as ongoing pregnancy surpassing 20 weeks gestation) of 25% for IVF and 19.3% for tubal surgery, and costs per ongoing pregnancy of £18 131 and £18 601 for IVF and tubal surgery respectively. This success rate for tubal surgery was higher than in much of the literature, but patient populations may not be comparable.

Donor oocyte IVF versus donor oocyte GIFT: In women ⩾40 years and with good ovarian reserve, donor oocyte GIFT was found to be more cost-effective than donor oocyte IVF (Silva *et al.*, 1998). The mean cost per delivery resulting from donor oocyte GIFT was estimated from local data at £17 311. This was compared with data previously reported for donor oocyte IVF of £22 300 (Legro *et al.*, 1997), and to the 1994 Society for Assisted Reproductive Technology (SART) data demonstrating a cost per delivery of between £17 562 and £21 953 for anonymous donor oocyte IVF (SART, 1996). This study was limited by the small number of women who had donor oocyte GIFT (22 women resulting in six deliveries).

ICSI versus donor insemination: Granberg *et al.* (1996), who performed a cost-effectiveness analysis in 1993–1994 comparing ICSI and donor insemination, found the costs per delivery to be greater for ICSI than for donor insemination (Granberg *et al.,* 1996). However, the authors stated that, given an increase of 34% in the cost-effectiveness of ICSI from 1993 to 1994, this procedure has the potential to become cost-effective when compared with other ARTs. Additionally, ICSI has the advantage of resulting in children who are genetically related to the father—a benefit that has not been captured in this cost-effectiveness analysis.

ICSI versus surgical treatment of varicocele: The development of ICSI has afforded men with severe sperm defects with an alternative to the treatment of varicocele. Schlegel (1997) conducted a modelling study using effectiveness data from controlled trials (Schlegel, 1997). High success rates of varicocelectomy made this the more cost-effective option. However, the length of follow-up was not stated and the high success rates quoted may not be generalizable. Furthermore, surgical treatment may be necessary in some patients to relieve pain.

ICSI versus vasectomy reversal: Four studies have been conducted to address the issue of post-vasectomy infertility (Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Donovan *et al.*, 1998; Deck and Berger, 2000). All four studies found that vasectomy reversal was more cost-effective than ICSI. In these studies the delivery rate following vasectomy reversal ranged from 17% (female partners aged >37 years) to 47% in more favourable populations, with costs ranging from £10 454 (Donovan *et al.*, 1998) to £19 306 (Deck and Berger, 2000) per delivery. For ICSI, the delivery rate ranged from 8% (female partners aged >37 years) to 56%, with costs ranging from £26 026 (Kolettis and Thomas, 1997) to £70 372 (Deck and Berger, 2000) per delivery. Apart from the study by Pavlovich and Schlegel (1997) (which included 710 cycles, but the number of was subjects not stated), these studies had small numbers of subjects ranging from 27 (Donovan *et al.*, 1998) to 55 men (Kolettis and Thomas, 1997).

Multiple comparisons: Philips *et al.* (2000) developed a series of decision–analytical models to reflect current diagnostic and treatment pathways for the five main causes of infertility (Philips *et al.,* 2000). Results of the modelling study suggested that for both tubal factors and endometriosis, IVF is the most cost-effective treatment option for severe disease, with surgery the most cost- effective in the case of mild or moderate disease. The authors suggested that ovulatory factors should be treated medically, with the addition of laparoscopic ovarian diathermy in the presence of PCOS. For other causes, stimulated IUI (unexplained and moderate male factor) and stimulated donor IUI (severe male) were considered cost-effective.

Complications of ART

Impact of multiple pregnancies: The increased incidence of multiple pregnancies and low birth weight due to ART generates increased demands on antenatal and neonatal services, long-term disability services, along with family resources, and this results in important economic implications.

Three studies (Liao *et al.*, 1997; Wolner-Hanssen and Rydhstroem, 1998; Miller *et al.*, 2000) have specifically examined the costs of these practices. Liao *et al.* (1997) compared neonatal outcomes in IVF programmes in Glasgow, Scotland before (1990) and after (1993) a policy change of transferring an average of two embryos had been implemented (Liao *et al.*, 1997). The policy change resulted in slightly lower clinical pregnancy and live birth rates, and a significant reduction in the rate of multiple pregnancy, preterm birth, and low birth weight babies in the 1993 group. The cost of neonatal intensive care in 1993 for babies born following IVF was about nine times lower than that in 1990. While the authors did not include indirect costs and wider societal costs, it may be assumed that these costs would increase in proportion to the number of multiple births. The study demonstrated that a policy of transferring two embryos to women in an IVF programme results in improved health for the women and their resulting children, decreased costs to the NHS, although a slight decrease in the live birth rate was observed.

In the UK, it is now recommended that only two embryos are transferred following IVF except in exceptional circumstances (Royal College of Obstetricians and Gynaecologists, 2001; Human Fertilisation and Embryology Authority, 2002). It is,

therefore, not surprising that the rate of twin pregnancy remains high. The routine transfer of one rather than two embryos would be expected to decrease the rate of twin pregnancies (and associated costs) at the cost of a lower live birth rate. Wolner-Hanssen and Rydhstroem (1998) compared actual (for two-embryo transfers) and hypothetical (for one-embryo transfers) take-home baby rates, twin pregnancies rates, and costs of sick leave and hospitalization during pregnancy, costs of deliveries, neonatal intensive care, and handicap care following transfer of one or two embryos (Wolner-Hanssen and Rydhstroem, 1998). These authors demonstrated that even when additional IVF cycles may be needed to achieve similar take-home baby rates after transfer of one compared with two embryos, the lower twin pregnancy rate of the former approach caused it to be more cost-effective than the latter. The study was limited, however, as the actual costs of single embryo transfer were not available to the authors.

Another approach taken to decrease the number of higher-order multiple births is multifetal pregnancy reduction. To address this issue, Miller *et al.* (2000) examined the birth outcomes and costs averted as a result of multifetal pregnancy reduction programme at one US hospital between 1986 and 1997 (Miller *et al.,* 2000). These authors demonstrated that rates of preterm delivery in multifetal pregnancies reduced to triplets and singletons were similar to those for unreduced triplets and singletons. The preterm delivery rate for reduced twins was lower than that for unreduced twins. The total estimated neonatal intensive care costs averted at that hospital over 11 years was £20.3 million, in contrast to the cost of £947 856 associated with the multifetal pregnancy reduction programme. The estimated hospitalization costs averted amounted to more than £19 million, or £42 654 per reduced pregnancy. This review did not find any studies relating to the intangible costs of the anguish to parents faced with the choice of pregnancy reduction or continuing with a high-order multiple pregnancy.

While higher-order multiples occur as a result of multiple embryo transfer following IVF, many multiples also result from drug-stimulated ovulation. No health economic papers were found that examined this factor, however.

Economic benefit studies

Current economic evaluations of ARTs in general—and of IVF specifically—are criticised for assuming that the only factor of importance to users is whether they leave the service with a child (Ryan, 1994). Such an approach ignores outcomes beyond a narrow medical definition of success, and the benefits that might accrue from the actual process of treatment (Ryan and Donaldson, 1996).

Several authors have used the willingness to pay (WTP) technique to address these concerns and have attempted to value both health and non-health benefits of IVF (Neumann and Johannesson, 1994; Granberg *et al.*, 1995; Ryan, 1994, 1996, 1997, 1998). The respondents in these studies were generally couples receiving IVF or other ART. In the USA, a study of potential childbearers (Neumann and Johannesson, 1994) found that the WTP to have a child ranged from £132 978 to £1.3 million, clearly exceeding most published studies on actual costs. In Sweden, Granberg *et al.* (1995) found that the range of WTP for a child was wide, from £0 to £30 000, and 55% of the couples were willing to pay £12 000 or more. In an Australian study, Ryan (1994, 1995) demonstrated an average WTP for IVF/GIFT services of £1399 per attempt, with a range of £237 to £11 167. Actual government expenditure per IVF cycle was £1204. A similar study by Ryan in Scotland (1997) found that a mean WTP for IVF of £5101, with a government expenditure of £2700 per cycle.

The majority of these benefit studies suffered from poor response rates. WTP suffers from the confounding influence of ability to pay and the fact that many of the respondents had already paid for infertility treatment. In addition, some respondents were, understandably, not willing to put a price on a child. A small number of studies used conjoint analysis in which respondents were asked to choose between two options with various characteristics. The relative crudeness of the attributes (e.g. attitudes of staff as 'good' or 'bad') makes interpretation difficult. A further problem is the difficulty of including dominant preferences in the analysis. Dominant preference occurs when a respondent always chooses in favour one attribute, such as the highest probability of pregnancy, even when all other factors weigh against that choice. Usually, such respondents are excluded from the analysis, although they may be reported separately. Nevertheless, these alternative techniques of benefit measurement have considerable potential to elucidate the factors of importance to infertile couples.

Macroeconomic perspectives

The costs of providing infertility services to a population compared with costs for other areas of health care is of interest to the health insurance market. Several American studies calculated total costs associated with the provision of infertility services to inform the decision-making process (Collins *et al.*, 1995; Rabin *et al.*, 1996; Hidlebaugh and O'Mara, 1997; Griffin and Panack, 1998; Stovall *et al.*, 1999; Blackwell, 2000; Blackwell *et al.*, 2001).

For the Massachusetts Health Maintenance Organization (HMO) an average ART cycle cost was estimated at £1.84 per member per annum, comparable with HMO costs for podiatry and nutrition, and far less than for physical therapy, organ transplants or mental health (Hidlebaugh and O'Mara, 1997). Collins *et al.* (1995) concurred, projecting the cost of adding IVF services to a typical employer health plan in 1995 at £1.98 per annum (Collins *et al.,* 1995). The latter authors also demonstrated benefit costs (the payments made by third-party payers, with all bad debts recycled) and premium costs (charges for premiums to cover the benefit, including health plan administration costs) of £6.19 and £6.95 respectively for a 300% increase in utilization, and £10.31 and £11.60 respectively for a 500% increase.

Additionally, three groups (Griffin and Panack, 1998; Stovall *et al.*, 1999; Blackwell, 2000) estimated infertility costs in the range of £0.39 to £0.73 per member per month (£1.31 per contract month in one study), and infertility services to consume between 0.41% and 0.79% of total health care costs. It is important to note that neither indirect costs nor neonatal costs

were included in these studies, and therefore the societal costs of providing infertility services were underestimated.

Rabin *et al.* (1996), by using financial modelling in a managed-care setting, determined break-even capitation rates to evaluate the cost impact of fertility care decisions. After determining an average cost per pregnancy of £5016 to £15 757, these authors found that as utilization of infertility services increased, the cost reductions no longer existed to offset increasing break-even capitation rates.

One Canadian study (Collins *et al.*, 1995) estimated the direct cost of infertility management; the annual cost of diagnosis and treatment was estimated at £1651 per couple, with a 26% live birth rate. The total annual cost of infertility management in Canada, approximately £247 million, would be 0.6% of the annual cost of health care.

In summary, it is important to note that although calculations for infertility costs need to include the costs for assisted reproduction procedures, the majority of couples who present for infertility care do not ultimately undergo assisted reproduction, even if an infertility policy includes cover for IVF treatment (Blackwell *et al.*, 2001).

Discussion

Overview

This report outlines the results of a review of the economic aspects of assisted reproductive technology in developed countries for the years 1990–2001 and, to our knowledge, is the first systematic review meeting these stated parameters in the field of ART. The review covers all aspects of ART for which recent economic studies have been published. In the process, it has highlighted common methodological limitations in the measurement and valuation of the costs and benefits of ART and gaps in the areas studied.

Key findings

The range of infertility diagnoses, population groups and ART interventions accepted for review in this study was considerable, and the variation in methods precluded quantitative analysis. However, consistent results were found in several categories, and are discussed below:

- Natural-cycle IVF has been claimed to be more cost-effective than stimulated-cycle IVF (Daya *et al*., 1995; Nargund *et al*., 2001), with reported costs for the latter approach being approximately 4-fold higher than for the former. However, it is not clear what was included in these cost estimates, bearing in mind that non-drug costs are the predominant cost burden in IVF practice. Caution is therefore required in interpreting these findings.
- Initiating treatment with IUI or stimulated IUI appears to be a more cost-effective option than immediate IVF for couples not experiencing severe male factor infertility or tubal factors (Peterson *et al.*, 1994; Zayed *et al.*, 1997; Goverde *et al.*, 2000; Van Voorhis *et al.*, 2001).
- For male infertility resulting from vasectomy, vasectomy reversal was found to be a more cost-effective treatment than ICSI (Kolettis and Thomas, 1997; Pavlovich and Schlegel, 1997; Donovan *et al.*, 1998; Deck and Berger, 2000). Donor insemination was also more cost-effective than ICSI (Granberg *et al*., 1996). Many couples may place a high value on having a genetically related child; this benefit of IVF was not included in the analysis comparing ICSI with donor insemination.
- For women with mild or moderate tubal disease, surgery may be a more cost-effective option than IVF, while the reverse may be true for women with severe tubal disease or severe endometriosis (Khare *et al.*, 1995; Copperman *et al.*, 1996; Mol *et al.*, 2001). The expertise of individual surgeons is likely to have an important impact on the success of both male and female surgical interventions.
- Not surprisingly, several patient characteristics have been shown to be associated with increased costs in the diagnosis and treatment of infertility. Increasing maternal age (especially after the age of 37 years) (Trad *et al*., 1995; Suchartwatnachai *et al*., 2000), decreased semen concentration (Van Voorhis *et al*., 2001), and increased severity of infertility diagnosis were shown in this review to be associated with decreased cost-effectiveness of selected interventions.

While the majority of studies accepted for this systematic review used multiple definitions of a successful outcome, including clinical pregnancy, delivery, live birth and take-home baby rates, all assumed the only factor critical to service users was whether they left with a baby. It is, presumably, this that compels individuals to seek treatment for infertility. However, to assess the costs and benefits of ART accurately, all factors that may influence utility, both positive and negative, should be considered. Five studies in this systematic review used the 'WTP′ technique or conjoint analysis to assess (dis)benefits of ART procedures, primarily IVF. It is interesting to note that a positive association existed between WTP and respondent income level, and that factors independent of a live birth were important to couples seeking treatment. In one study, for example, attitudes of staff were more important than a 5% increase in success rates (Ryan, 1995, 1999). Future studies would be improved by a more inclusive accounting of user benefits from infertility services.

Limitations of the included studies

The majority of included studies met between 50 and 80% of the quality requirements. For both full economic evaluations and costing studies, it is worth noting that ~75% of the studies did not include indirect costs (costs arising from lost productivity). Measuring and valuing these wider societal costs is particularly appropriate because couples seeking infertility treatment may be highly productive in the workforce, and the potential productivity loss to society may be great. When indirect costs were included, the studies generally accounted for lost productivity arising from treatment procedures alone and failed to include those arising from ART complications, especially multiple births.

Nearly half of the economic studies reviewed were conducted in the USA where charges are often used as proxies for costs and where the unique organization of health care services may make it difficult to generalize the results to other industrialized

countries. Publication bias, in which studies reporting successful outcomes are more likely to be published than reports of unsuccessful interventions, also has implications for generalizability.

Less than half of the included studies included sensitivity analysis. The failure to analyse the uncertainty surrounding key economic parameters leaves the reader unable to judge the degree to which the conclusions of these studies are meaningful and robust (Briggs *et al.*, 1994). However, reviews of economic evaluations in other areas of medicine have revealed similar levels of quality (Petrou *et al*., 2000; Whitten *et al*., 2002).

When interpreting economic evaluations of ART, inherent difficulties exist arising from the variability in outcome measures used, spontaneous or background pregnancy rates, and patient selection. ART effectiveness rates—referred to as 'success rates'—may appear either optimistic or dismal depending on the numerators and denominators used in the analysis. To allow for comparisons, authors must clearly define the numerators and denominators of success rates. The majority of studies included in this systematic review relied on one or more of the following reproductive outcomes: biochemical pregnancy, clinical pregnancy, ongoing pregnancy, live birth rate, maternity rate and take-home baby rate. Direct comparisons are made problematic with varying definitions. For example, IVF consists of a series of stages with 'drop-outs' possible. Success rates may be given per started cycle or per completed cycle. Using embryo transfer cycles as the denominator will appear to increase the success rate, while using all started treatments (which use the woman as the denominator) will appear to decrease the rate. Similarly, if clinical pregnancies are used as the measure of success, then spontaneous abortion, ectopic pregnancy, stillbirth and preterm birth are all considered successes. Some studies used number of live births, or 'take-home' babies, as an outcome measure (e.g. Stern *et al*., 1995), but this overstates the success rate because multiple births are counted as multiple 'successes' unless methods are used to take account of this.

One of the main problems with ART to date remains the high incidence of multiple pregnancies. These carry a higher risk of maternal and perinatal mortality and morbidity, especially as a result of preterm delivery. While several studies did include the costs associated with multiple births, the viewpoint of many of the studies was limited to that of the provider of health care, was generally short-term, and rarely went beyond the immediate postnatal period. Long-term consequences require evaluation from an economic perspective, and include, but are not limited to: costs associated with disability; day care services and respite care; adaptations to an infant's home; and incremental expenditures on health and non-health goods as a result of their impaired health status. In addition, none of the included studies estimated costs associated with the intangible psychological consequences associated with multiple birth, especially higher-order multiples. These include depression, marital discord and increased stress levels and warrant inclusion in future economic studies (Henderson and Petrou, 1999).

This systematic review has shown that, despite significant methodological limitations, consistent findings have been reported in several areas. It has also revealed gaps in the literature. The main area where further research is required is in the long-term costs associated with prematurity, and whether costs and consequences are different for naturally occurring multiples compared with ART multiples.

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