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An international survey of the health economics of IVF and ICSI

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The health economics of IVF and ICSI involve assessments of utilization, cost, cost-effectiveness and ability to pay. In 48 countries, utilization averaged 289 IVF/ICSI cycles per million of population per annum, ranging from two in Kazachstan, to 1657 in Israel. Higher national utilization of IVF/ICSI was associated with higher quality of health services, as indicated by lower infant mortality rates. IVF and ICSI are scientifically demanding and personnel-intensive, and are therefore expensive procedures. The average cost per IVF/ICSI cycle in 2002 would be US$9547 in the USA, and US$3518 in 25 other countries. Price elasticity estimates suggest that a 10% decrease in IVF/ICSI cost would generate a 30% increase in utilization. The average cost-effectiveness ratios in 2002 would be US$58 394 per live birth in the USA, and US$22 048 in other countries. In three randomized controlled trials, incremental costs per additional live birth with IVF compared with conventional therapy were US$ –26 586, $79 472 and $47 749. The national costs of IVF/ICSI treatment would be US$1.00 per capita in one current model, but the costs to individual couples range from 10% of annual household expenditures in European countries to 25% in Canada and the USA.

Key words: cost/cost-effectiveness/health economics/IVF/utilization

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Introduction

IVF and ICSI are effective treatments for Fallopian tube obstruction, severe male infertility and persistent infertility after conventional treatments have failed (ESHRE Capri Workshop Group, 1996). Both treatments are costly because of the need for highly trained personnel and expensive equipment, which is often the case with new health technologies. Unfortunately, the cost of IVF and ICSI is more than some infertile couples are able to pay, and this tends to limit access to this treatment. Thus, although the prevalence of infertility and the need for IVF and ICSI is similar from country to country, the international availability of IVF services is highly variable. For example, IVF and ICSI services were available in only 45 (24%) of the 191 member states of the World Health Organization (WHO). The 45 countries accounted for 78% of the world's population, and 91% of the world's gross domestic product (Collins, 2002).

This overview of the health economics of IVF and ICSI will focus on utilization, cost, cost-effectiveness and ability to pay, from a societal perspective. The scope of the overview is international, to investigate reasons for the inequalities in utilization and cost which exist between nations, despite the similar prevalence of infertility.

Methods

English language publications were searched in MEDLINE, and 6000 citations in the author's reference manager, using keywords for IVF, ICSI, cost and cost-effectiveness. Subsequent bibliographies were cross-referenced, but no hand searches were conducted of journals or meeting proceedings. Relevance was determined after review of the abstracts and validity was evaluated by study design. The evidence from randomized controlled trials was selected where choices existed.

Table I. IVF/ICSI centres per million population

Country	No. of IVF centres	Centres per 10^6 population	Country	No. of IVF centres	Centres per 10^6 population
Argentina	14	0.39	Jordan	11	1.74
Australia	27	1.46	Kazachstan	1	0.06
Austria	25	3.07	Rep. of Korea	93	2.02
Belgium	25	2.47	Lebanon	3	0.94
Brazil	104	0.63	Malaysia	4	0.19
Canada (2001)	23	0.75	Mexico	9	0.09
China	20	0.02	Netherlands	13	0.83
Czech Republic	15	1.46	Norway	8	1.81
Denmark	16	3.04	Pakistan	2	0.01
Egypt	30	0.45	Poland	5	0.13
Finland	20	3.88	Portugal	15	1.52
France	140	2.39	Russia	18	0.12
Germany	100	1.22	Saudi Arabia	17	0.84
Greece	46	4.34	Singapore	6	1.73
Hong Kong	6	0.98	Slovenia	2	0.38
Hungary	10	0.99	Spain	114	2.88
Iceland	1	3.62	Sweden	15	1.69
India	39	0.04	Switzerland	17	2.33
Indonesia	3	0.01	Taiwan	65	3.05
Ireland	6	1.63	Thailand	4	0.07
Iran	69	1.05	Turkey	32	0.50
Israel	22	3.68	UK	75	1.28
Italy	168	2.93	USA	360	1.31
Japan	377	2.99	Venezuela	8	0.34

Utilization of IVF and ICSI services

Utilization of a given health service is a key component of health economics because it depends in part on the cost of the service, regardless of whether the payment comes from the private or the public purse. When individuals have to pay, some will be unable to afford a given service; when public or private insurers pay, competing priorities may dictate that expensive new services must be rationed or passed over. Need, demand, availability and access are inter-related, and influence the level of utilization. The need for service is determined by the prevalence of the health problem; demand for the service is defined by the motivation to have treatment; availability is a product of public and private health policies controlling the level of personnel, equipment and facilities; and access to the available service is determined by factors such as the cost to the individual, distance and opening hours. Utilization is the actual consumption of the health service in a given period of time. The overall or national cost of a given health service is the cost per service multiplied by the utilization of the service (Drummond *et al.*, 1987).

The potential need for IVF services is high because IVF and ICSI treatment is the only effective recourse for many couples with severe tubal and seminal infertility, or longstanding infertility after conventional treatment. Although the level of need may be 3000 IVF/ICSI cycles per million population per annum (c.p.m. pa), optimal demand is estimated to be 1500 c.p.m. pa because only 50% of infertile couples take up consultation and treatment services for infertility (ESHRE Capri Workshop Group, 2001). The availability of IVF/ICSI services can be estimated from the number of centres that provide IVF/ICSI services. Cost and other factors limit access to the centres, however, so that IVF/ICSI utilization (the number of cycles per million population per annum) is determined only in part by IVF/ICSI availability (the number of centres per million population).

Availability of IVF and ICSI centres

The availability of IVF and ICSI was surveyed in 33 countries by the International Federation of Fertility Societies in December 2000 (Jones and Cohen, 2001). Availability in a further 14 countries has been reported from other sources (Schenker and Shushan, 1996; de Mouzon and Lancaster, 1997; Granberg *et al.*, 1998; EIM Programme, 1999). Data for Canada are from a Canadian Fertility and Andrology Society press release in October 2001. A total of 2203 IVF/ICSI centres has been reported from 48 countries, an estimated average of 0.50 centres per million population within the 48 reporting countries, or 0.37 centres per million population in all of the 191 WHO member countries. The range was from 0.01 IVF/ICSI centres per million population in Indonesia and Pakistan up to 4.34 in Greece (Table I).

What national health and economic factors influence the availability of IVF and ICSI services? Fertility rates, infant mortality rates, gross domestic product per capita, health spending as a percentage of the national budget and the proportion of health spending from government sources were included in the World Health Report 1999 (World Health Organization, 2000). In a multiple regression analysis, only infant mortality was significantly associated with availability, accounting for 36% of the variability in IVF/ICSI centres per million population. In the 48

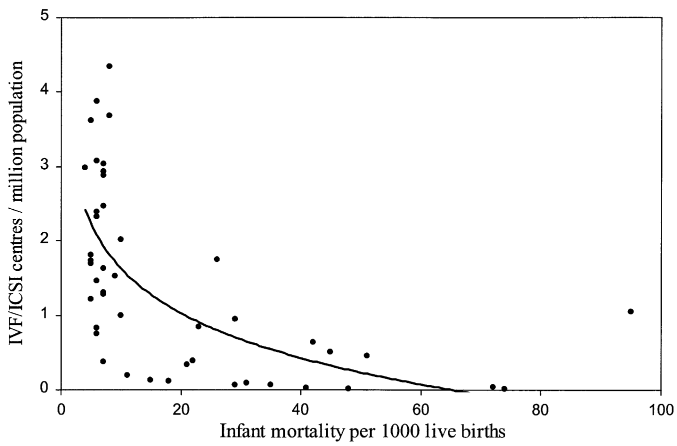

Figure 1. Availability of IVF centres and infant mortality by country.

countries, there was one additional IVF/ICSI centre per million population for every four fewer infant deaths in the first year of age per 1000 live births in 1998 (P = 0.0001). Overall, 14 of 16 countries with infant mortality rates greater than 20 per 1000 have less than one IVF/ICSI centre per million population (Figure 1). As noted above, the availability of a health service is a function of healthcare policy. With national or public insurance, government policy makers attempt to apportion personnel, equipment and facility resources in a fair manner so that competing healthcare needs can be met within the bounds of the available funds. Where private insurers and individuals pay for healthcare, the availability of elective services such as IVF/ICSI depends on whether insurers or care providers can charge enough for the personnel, equipment and facilities to break even, or preferably, ensure a profit. Thus, it is notable that the availability of IVF/ICSI services is associated, at a national level, with lower infant mortality rates, and not with wealth (gross domestic product), overall spending on health, or the government proportion of overall health spending. Lower infant mortality is considered to reflect better overall quality of a national healthcare programme (Wise and Pursley, 1992). Countries with more than 20 infant deaths per 1000 live births per annum would be expected to place a lower priority on IVF and ICSI availability.

Uptake of IVF and ICSI cycles

IVF/ICSI cycles per annum have been reported for 33 countries (Schenker and Shushan, 1996; de Mouzon and Lancaster, 1997; Health Council of the Netherlands: Committee on *In vitro* fertilization, 1997; Granberg *et al.*, 1998; EIM Programme, 1999), whilst data for Canada are from a current survey in the author's files. For the remaining countries, cycles per annum were estimated by multiplying the number of IVF/ICSI centres by the average number of cycles per annum per centre (287) in the countries for which cycles per annum and centres were reported. There were an estimated total of 334 386 IVF/ICSI cycles per annum in 48 countries, approximately 289 cycles per million population per annum within the 48 reporting countries, or 57 c.p.m. pa in all WHO country member states. The four lowest countries were Kazachstan, Pakistan, Indonesia and China with two, four, four and five IVF/ICSI c.p.m. pa respectively, and the highest country was Israel with 1657 c.p.m. pa. (Table II).

Higher utilization of IVF and ICSI cycles also was associated with lower infant mortality. In a multiple regression analysis, only infant mortality was significantly associated with utilization, accounting for 29% of the variability in IVF/ICSI c.p.m. pa. In the 48 countries, there is one additional IVF/ICSI c.p.m. pa for every seven fewer infant deaths in the first year of age per 1000 live births in 1998 ($P = 0.0007$). As Figure 2 shows, 15 of 16 countries with infant mortality rates greater than 20 per 1000 have less than 500 IVF/ICSI cycles per million population per annum.

The estimated utilization of IVF/ICSI cycles per annum per million population was less than the proposed optimal level of demand (1500 c.p.m. pa) in all countries but Israel. Utilization was less than 150 c.p.m. pa (10% of the estimated optimal level of demand) in 21 countries, and more than 750 c.p.m. pa (50% of the estimated level) in only three countries. The range of utilization in North America (from 27 to 190 c.p.m. pa) is below the range in Western Europe (from 99 to 829 c.p.m. pa).

A search for associations among indicators of national economic and health status is subject to several sources of error. For example, average data were imputed for IVF/ICSI utilization in countries which lacked data on IVF/ICSI cycles per annum; also, data were collected from 1995 to 2000. Furthermore, data for national economic and health indicators were collected in different years from several data sources. Variability in the national data between countries is tolerable, however, because each indicator was collected in the same year for all countries (World Health Organization, 2000). Notwithstanding these sources of potential error, the regression equations have isolated a single strong association between an indicator of good national health programmes and both the availability and the utilization of IVF/ICSI services.

Cost of IVF and ICSI treatment

International costs of IVF and ICSI cycles

IVF and ICSI treatments are costly technologies that involve several professions and expensive laboratory facilities (U.S. Congress Office of Technology Assessment, 1988). The direct costs of a cycle of IVF treatment arise from the medical consultation and visits, drugs, laboratory charges (general, hormone and embryology), ultrasound procedures, IVF procedures (oocyte retrieval and embryo transfer), hospital charges, nurse coordinator costs, administrative charges and fees for anaesthesia. Indirect costs include lost time from employment and travel costs, which are difficult to estimate. Published IVF/ICSI cost estimates frequently omit indirect costs, but this is a minor defect because indirect costs are relatively unimportant in IVF/ICSI cycles. For example, indirect costs comprised $361 of the $5466 total costs in the IVF treatment group of a Canadian randomized controlled trial (RCT) comparing IVF and standard therapy (Goeree *et al.*, 1993)

Estimates of IVF and ICSI costs are often a simple report from service providers giving total charges per cycle of treatment. Charges per cycle do not take into account the reduced costs associated with cycles which do not reach retrieval and embryo transfer. Less frequently, and usually in the context of an RCT, the actual cost of each component of the service is estimated for all cycles or a sample of cycles. When comparing published IVF

Table II. IVF/ICSI cycles per million population per annum (c.p.m. pa)

Country	No. of IVF/ICSI cycles	C.p.m. pa	Country	No. of IVF/ICSI cycles	C.p.m. pa
Argentina	4018	111	Jordan	3157	501
Australia	7749	418	Kazachstan	35	2
Austria	809	99	Rep. of Korea	9691	210
Belgium	4038	398	Lebanon	861	270
Brazil	29 848	180	Malaysia	1148	54
Canada 2000	5800	190	Mexico	2583	27
China	5740	5	Netherlands	13 000	829
Czech Republic	4195	408	Norway	2825	639
Denmark	3760	713	Pakistan	574	4
Egypt	841	13	Poland	972	25
Finland	3418	663	Portugal	4305	436
France	35 801	610	Russia	3715	25
Germany	34 216	417	Saudi Arabia	4879	242
Greece	5088	480	Singapore	1065	306
Hong Kong	890	146	Slovenia	1565	295
Hungary	1469	145	Spain	2897	73
Iceland	248	899	Sweden	5979	674
India	11 193	11	Switzerland	1753	240
Indonesia	861	4	Taiwan	3140	147
Ireland	572	155	Thailand	1148	19
Iran	19 803	301	Turkey	2383	37
Israel	9913	1657	UK	25 878	441
Italy	1065	19	USA	34 448	126
Japan	12 754	101	Venezuela	2296	99

and ICSI cycle costs it is important to determine whether each estimate includes drug charges as well as facility charges. Also, published estimates of IVF/ICSI costs may not include the downstream costs of IVF/ICSI cycles. The most significant downstream costs arise from multiple births due to the hospital costs of the premature births and the associated neonatal complications.

The majority of reports on the cost of IVF and ICSI services are cost descriptions which do not include an outcome assessment or comparison with an alternative policy (U.S. Congress Office of Technology Assessment, 1988; Neumann *et al.*, 1994; Collins *et al.*, 1995; Trad *et al.*, 1995; van Voorhis *et al.*, 1995; Fluker and Tiffin, 1996; Goldfarb *et al.*, 1996; Schenker and Shushan, 1996; Granberg *et al.*, 1998; Mantovani *et al.*, 1999; Goverde *et al.*, 2000; Philips *et al.*, 2000). The currency and year of the estimates vary, and data are missing for 22 of the 48 countries for which utilization estimates were available. In projecting each estimate forward to 2002 it would be preferable to use a country-specific inflation factor for private or public healthcare service expenditures. Unfortunately, healthcare cost inflation data are not available for most countries.

The median charge for a single cycle of IVF in the United States in 1986 was $4688 (U.S. Congress Office of Technology Assessment, 1988). In 1991–1992, the Ohio cost per cycle, adjusted for incomplete cycles was $6332 (Goldfarb *et al.*, 1996), whilst based on 1992 data from Iowa, the estimated cost per IVF cycle was $8071 (van Voorhis *et al.*, 1995). In 1993, the cost per cycle in Boston was estimated to be $8000 (Trad *et al.*, 1995). A 1993 survey of 71 IVF clinics in the USA found that the mean

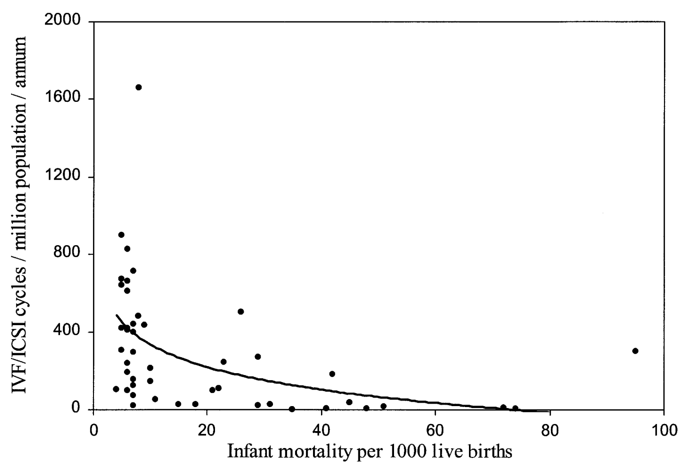

Figure 2. Utilization of IVF/ICSI services by infant mortality and country.

charge for a single completed IVF cycle was $7861, whilst the cost after adjusting for incomplete cycles was $6233 (Collins *et al.*, 1995). In 1994, the cost per cycle based on six sites in eastern states was $8000; only $280 was deducted for incomplete cycles (Neumann *et al.*, 1994).

The USA estimates of IVF costs were projected to 2002 according to trends in healthcare cost inflation in that country (U.S. Bureau of the Census, 1997).The average cost per IVF cycle, projected to 2002 would be US$9547 (95% CI $8249 to $10 846), based on six previously published estimates. The range would be from $8129 to $11 385 (U.S. Congress Office of

Table III. Cost or charges per IVF cycle

Country	Cost per cycle	Original currency	Year of estimate	US 2002 cost ($)	Reference
Canada	5700	CAD	1995	4532	Fluker *et al.* (1996)
Netherlands	3350	Guilders	1995	2042	Goverde *et al.* (2000)
Denmark	1900	Sterling	1994	3753	Granberg *et al.* (1998)
Finland	1300	'	'	2568	'
Iceland	2000	'	'	3950	'
Norway	1800	'	'	3555	'
Sweden	2100	'	'	4148	'
Italy	5.85	Lira[a]	1997	4326	Mantovani *et al.* (1999)
UK	1717	Sterling	1998	2955	Phillips *et al.* (2000)
China	1500	USD	1995	1908	Schenker and Shushan (1996)
Hong Kong	5000	'	'	6361	'
India	2000	'	'	2545	'
Indonesia	3000	'	'	3817	'
Iran	1000	'	'	1272	'
Israel	3000	'	'	3817	'
Japan	2500	'	'	3181	'
Jordan	1500	'	'	1908	'
Korea	1100	'	'	1400	'
Lebanon	4000	'	'	5089	'
Malaysia	4500	'	'	5725	'
Pakistan	1000	'	'	1272	'
Saudi Arabia	4000	'	'	5089	'
Singapore	4500	'	'	5725	'
Taiwan	3000	'	'	3817	'
Thailand	2500	'	'	3181	'

[a]millions.
CAD = Canadian dollars; USD = US dollars.

Technology Assessment, 1988; Neumann *et al.*, 1994; Collins *et al.*, 1995; Trad *et al.*, 1995; van Voorhis *et al.*, 1995; Goldfarb *et al.*, 1996).

The cost of a single IVF cycle from 25 other countries is shown in Table III. The year and currency of the original estimate are listed, together with the corresponding equivalent estimates for 2002 in US$ (Fluker and Tiffin, 1996; Schenker and Shushan, 1996; Granberg *et al.*, 1998; Mantovani *et al.*, 1999; Goverde *et al.*, 2000; Philips *et al.*, 2000). Two of these estimates (Goverde *et al.*, 2000; Phillips *et al.*, 2000) were based on actual expenditures, whilst one study (Granberg *et al.*, 1998) reported costs for public and private sectors, with the listed costs being the weighted average for each of the five countries. The remaining estimates were based on surveys in which respondents were asked to state charges for IVF cycles.

The original estimates in guilders, sterling and lira were projected to 2002 and then converted to US dollars. Because data for healthcare inflation rate in the original countries could not be found, the inflation projection to 2002 was based on the average inflation in healthcare expenditures in the USA (3.5%) (U.S. Bureau of the Census, 1997). The 1995 Canadian estimate was projected to 2002 using the inflation rate for household expenditures on health in Canada (5.5%) and the 2002 result (CA$ 7252) was converted to US$ at an exchange rate of 1.60 (Chaplin and Earl, 2000).

The mean cost of an IVF cycle in 25 countries other than the USA, projected to 2002, would be equivalent to US$3518 (95% CI $2924 to $4111), based on 25 previously published estimates. The estimates ranged from US$1272 in Pakistan to US$6361 in Hong Kong. The mean cost per IVF cycle in other countries is approximately 37% of the cost in the USA.

The estimates listed in Table III do not include the cost of ICSI procedures. In the UK, the estimated cost of an IVF cycle in 1998 was £1717, and the added cost of ICSI was £300, which meant that ICSI cycles were 17% more costly than IVF cycles without ICSI (Philips *et al.*, 2000). In the USA in 1995, the overall cost of an IVF cycle with ICSI was $11 818 (Pavlovich and Schlegel, 1997), which was 69% higher than the average reported IVF costs, projected to 1995 (Fluker and Tiffin, 1996; Schenker and Shushan, 1996; Granberg *et al.*, 1998; Mantovani *et al.*, 1999; Goverde *et al.*, 2000; Philips *et al.*, 2000).

Utilization and cost of IVF and ICSI treatment

The Rand experiment confirmed the relationship between cost to the consumer and utilization of health services by showing that the use of healthcare services declined when cost sharing rose from zero to 25% of the total cost (Manning *et al.*, 1987). It is reasonable to argue, therefore, that if the cost of IVF services were lower, increased utilization of IVF services might be expected. The collected international data on the utilization of services and cost of IVF cycles provide an insight into the possible extent of such increases in utilization. The relationship is defined by price elasticity: the change in volume of services in response to change in prices to the consumer. In 25 countries for which utilization and cost information were available, the following formula was applied:

$$\text{elasticity} = \frac{\%\ \text{change in quantity of service}}{\%\ \text{change in price to consumer}}.$$

Under market conditions, if the cost of IVF services decreased, utilization would be expected to increase, giving rise to an inverse relationship which would be denoted by a negative sign. As an example, the UK can be compared with the USA (Manning *et al.*, 1984). The UK has 441 c.p.m. pa, and average 2002 costs are US$2955 per cycle, whilst the USA has 126 c.p.m. pa and 2002 costs per cycle are US$9547. The UK cost is 69% lower, and utilization is 2.5-fold higher than in the USA; hence, the price elasticity is –2.50/0.69, or –3.62. The average price elasticity calculated from the ratio of the differences in IVF cycle costs and IVF utilization in 24 countries relative to the USA is –3.18. This is an extremely high level of responsiveness to changes in IVF cycle costs: a 10% reduction in cost per IVF cycle would be associated with a 32% increase in utilization of IVF cycles. Nevertheless, 32% is within the range of a 1995 estimate based on the level of co-payment for IVF cycles, in which a 10% reduction in consumer share of cycle cost appeared to generate a 22–43% increase in utilization (Collins *et al.*, 1995).

The magnitude of the theoretical effect of reduced costs on IVF uptake is much greater than the findings of the original Rand experiment, which concerned mainly ambulatory care (Enthoven, 1984). Whether to utilize IVF treatment may seem to be a more elective choice for the consumer than the average health service documented in the Rand experiment. The higher cost may also serve as a more powerful deterrent to IVF usage. Moreover, other factors may influence IVF utilization, such as clinical and regulatory policies governing access to IVF and more favourable public and professional attitudes toward IVF services. In any case, the IVF cycle costs on which the present calculations were based are not necessarily borne by the individual consumer. Depending on the country, the actual cost to the consumer varies from virtually zero to 100% of the amounts listed in Table III. Unfortunately, there is no formal collection of country-by-country information on the proportion of IVF cycle costs that is paid by infertile couples. If that were available, the price elasticity co-efficient might be even higher.

Cost-effectiveness of IVF treatment

Cost-effectiveness ratios

The term cost-effectiveness expresses the relationship between cost and outcome, which in the present context is cost per live birth. The calculation is straightforward: cost divided by live birth rate. In IVF treatment the usual ratio is cost per cycle divided by the proportion of cycles that gave rise to a live birth. This cost-effectiveness ratio can be derived from the analysis of a case series provided that both costs and delivery or live birth rate per cycle have been estimated. Frequently, however, cost-effectiveness ratios for IVF treatment are reported as cost per pregnancy rather than cost per live birth. To adjust such reports to live birth rates involves multiplying pregnancy rates by a factor that approximates to 80%.

Cost-effectiveness ratios have been reported from the USA (five estimates) and seven other countries (Neumann *et al.*, 1994; Trad *et al.*, 1995; van Voorhis *et al.*, 1995; Goldfarb *et al.*, 1996; Granberg *et al.*, 1998; Karande *et al.*, 1999; Mantovani *et al.*, 1999; Goverde *et al.*, 2000). The average cost per delivery in a 1992 estimate from Iowa was $44 200 (van Voorhis *et al.*, 1995), whilst the 1992–1993 costs per delivery in Ohio were estimated as $35 330 (Goldfarb *et al.*, 1996). The 1993 cost per delivery in Boston was $29 120 (Trad *et al.*, 1995), whilst in 1994 the average cost per delivery in the northeastern USA was $66 667 (Neumann *et al.*, 1994). The 1996–1997 cost per pregnancy in Illinois was $38 021, or approximately $47 500 per delivery (Karande *et al.*, 1999). These estimates were projected to 2002 following trends in healthcare cost inflation in the USA (U.S. Bureau of the Census, 1997). The mean cost-effectiveness ratio based on USA estimates is US$58 394 per live birth (95% CI $36 080 to $80 708), the range being $39 688 to $87 788.

Cost-effectiveness for public and private sectors have been reported from five Scandinavian countries (Granberg *et al.*, 1998). The average cost-effectiveness ratios in 1994, weighted by volume of public and private cycles, were £10 295, £11 858, £13 413, £11 211 and £7400 per delivery in Sweden, Denmark, Norway, Finland and Iceland respectively. A cost-effectiveness ratio reported from the Netherlands in 1995 was 27 409 guilders per IVF delivery, developed within an RCT and based on actual expenditures (Goverde *et al.*, 2000). The cost-effectiveness ratio in Italy during 1997 was 41.4 million lira, developed within a pharmaco-epidemiological model (Mantovani *et al.*, 1999). The original estimates in guilders, sterling and lira were projected to 2002, based on the average inflation in healthcare expenditures in the USA (3.5%), and then converted to US dollars (U.S. Bureau of the Census, 1997). The mean cost-effectiveness ratio based on non-USA estimates is US$22 048 per live birth (95% CI $16 957 to $27 138), the range being $14 617 to $30 618.

Cost-effectiveness analyses

A cost-effectiveness analysis compares the costs and effects of one activity with those of another. It is the most common type of full economic analysis, a category that includes cost utility analysis and cost–benefit analysis (Drummond *et al.*, 1997). Cost-minimalization analysis is a type of cost-effectiveness analysis in which the outcomes are known to be equivalent and the lowest cost alternative would be the preferred choice. The less common types of economic analysis, which are rarely used in the assessment of IVF or ICSI treatment, are discussed briefly in the next section.

Cost-effectiveness analysis measures outcomes in the most appropriate natural units, such as years of life gained, lives saved, functional improvement, proportion of cases treated successfully or events prevented by the intervention of interest. In the case of IVF, successful treatment produces events rather than prevents them. Natural outcome units make clinical sense, but the diversity of possible outcomes precludes comparing the cost-effectiveness of treatment for different types of disease (Torgerson and Raftery, 1999).

In considering a cost-effectiveness analysis, the important methodological issues include whether direct and indirect costs were measured, and whether the effects of events occurring in the future have been discounted. As noted above, indirect costs of IVF treatment arising from lost wages and travel expenses are difficult to quantify; when measured, indirect costs appeared to be minor (Goeree *et al.*, 1993). The issue of discounting is also relatively unimportant in economic analyses of IVF treatment because the effects occur within a short period of time (Drummond *et al.*, 1987).

If the lower cost treatment yields higher benefits, the choice is simplified and the lower cost therapy is said to dominate the higher cost therapy. Usually, however, the better outcomes are achieved only at higher cost and it is desirable to know the additional cost for each additional unit of benefit. Thus, the key computation in cost-effectiveness analysis is the marginal or incremental cost of the benefit of interest. The calculation involves dividing the difference in cost by the difference in effect.

The internal validity of a cost-effectiveness analysis depends on the design of the comparison of effects; therefore the highest-ranking studies are those in which the cost analysis has been carried out within the context of an RCT (Drummond *et al.*, 1997). Nevertheless, because economic analyses are intended for broad clinical application, the effectiveness assessment should correspond closely with clinical practice, which is not always the case in RCTs. While a single RCT has high internal validity, the results of the trial may not generalize readily to other settings. Combining a cost analysis with effectiveness data from a systematic review of effectiveness involving trials from several settings may offer a more precise estimate of effectiveness, which can more readily be generalized. A third alternative is to nest the cost analysis within a modelling exercise involving evidence from medical care research and administrative data.

RCT-based analysis of IVF cost-effectiveness

Although numerous RCTs have compared the cost-effectiveness of different down-regulation, stimulation or transfer protocols within IVF cycles, only three RCTs have evaluated the cost-effectiveness of a programme of IVF treatment versus standard therapy. Accrual for the first of these RCTs took place in the 1980s; the effectiveness of IVF and the alternative standard therapy have improved since that time (Goeree *et al.*, 1993; Jarrell *et al.*, 1993; Soliman *et al.*, 1993). This Ontario trial compared two protocols among couples on a waiting list for IVF treatment: one stimulated treatment cycle (without embryo freezing); or a 6-month period of untreated observation or elective conventional therapy including ovulation induction and intrauterine insemination (IUI), in the control group. Direct costs obtained from hospital sources and patient interviews in 1992 were CA$5106 and $1529 in the early and delayed IVF groups respectively (Goeree *et al.*, 1993). Live birth rates were approximately 10% and 6% in the early and delayed IVF groups respectively. Thus, the marginal cost of a single additional live birth with early IVF treatment in Canadian dollars was ($5106 – $1529)/(0.10 – 0.06) = $89 427, which in 2002 would be approximately US$79 472.

An RCT in Illinois compared IVF as the initial infertility treatment and a standard protocol of diagnosis and therapy among couples enrolling for the first time in an infertility clinic (Karande *et al.*, 1999). The standard protocol involved three clomiphene cycles and three gonadotrophin cycles followed by four IVF cycles. The 50 couples allocated to standard therapy had 76 clomiphene cycles, 34 gonadotrophin cycles and 10 IVF cycles. The 46 couples allocated to IVF therapy had 34 IVF cycles (23 couples, 0.74 cycles per couple) and 14 cryopreservation cycles. Pregnancy rates after 22 months of observation were 35% (16/46 couples) in the IVF group and 56% (28/50 couples) in the standard protocol group ($P = 0.037$). The IVF pregnancies included those from cryopreservation and donor cycles and spontaneous pregnancies; the standard protocol group included nine spontaneously occurring pregnancies. Direct costs obtained from billing information during 1995–1997 were US$13 225 in the early IVF group and $9557 in the standard therapy group. Thus, the marginal cost of a single additional live birth with early IVF treatment was [1.25 × ($13,225 – $9557)/(0.35 – 0.56)] = US$ –21 627, which would be approximately US$ –26 586 in 2002. IVF was dominated by the standard therapy alternative because IVF was more expensive, with less benefit.

An RCT in the Netherlands compared six cycles of IUI alone, six cycles of IUI with ovulation stimulation, or six cycles of IVF among couples with unexplained or male infertility (Goverde *et al.*, 2000). More couples completed the allotment of cycles in the IUI groups (338 IUI cycles, 3.9 per couple and 355 FSH/IUI cycles, 4.2 per couple) than in the IVF group (270 IVF cycles, 3.1 per couple). After 3.5 years, the live birth rates per cycle were 7.4, 8.7 and 12.2% in the IUI, FSH/IUI and IVF groups respectively. The direct hospital and out-patient costs per cycle in Dutch guilders (NLG) were 623 NLG, 931 NLG and 3350 NLG in the IUI, FSH/IUI and IVF groups respectively. The live birth rates per couple were 29.1, 36.5 and 37.9% in the IUI, FSH/IUI and IVF groups respectively. The reported effectiveness and cost data are shown in the first four columns of Table IV. Incremental cost-effectiveness ratios calculated from the authors' data are shown in the last two columns of the table.

Economic data collected prospectively during a well-designed RCT have high internal validity, although the results may not generalize, as in the three IVF cost-effectiveness analyses under discussion. IVF effectiveness generally exceeded the level in the Ontario trial by the time the trial was reported (Jarrell *et al.*, 1993). In the Illinois trial, the uptake of IVF was only 50% in the early IVF group because the infertile couples were not yet ready for IVF (Karande *et al.*, 1999). The Netherlands trial evaluated a protocol of six IVF cycles, although few couples undergo more than three cycles (Health Council of the Netherlands: Committee on *In vitro* fertilization, 1997; Meldrum *et al.*, 1998). In this trial, the results by couple for IVF compared with both IUI and FSH/IUI treatment would be more comparable with the other two RCTs: for that comparison, the 2002 incremental cost-effectiveness ratio would be US$47 749. The calculated incremental cost-effectiveness ratios are widely dissimilar, although the design quality, interventions and diagnostic categories were comparable in the three trials (Table V). There were three distinct health economic systems, variable couple characteristics and different numbers of cycles in the IVF groups (one or two cycles, and six cycles), all of which may account in part for the cost-effectiveness results. With respect to couple characteristics, the average duration of infertility was approximately 4 years in the Ontario and Netherlands trials, and just over 2 years in the Illinois trial. Each year of infertility alters the likelihood of IVF conception by 2%, and the likelihood of standard therapy conception by 12% (Collins *et al.*, 1984; Templeton *et al.*, 1996; Templeton and Morris, 1998). Thus, the short duration of infertility would favour the couples in the standard treatment group more than the IVF group, leading to the better pregnancy rate and dominance of standard treatment in the Illinois trial.

Table IV. Incremental cost-effectiveness ratios: IUI, FSH/IUI and IVF treatment.

	Direct costs (NLG)		Live birth rate (%)		Incremental cost[a]	
	IVF	Other	IVF	Other	NLG (1995)	USD (2002)
Per cycle	3350	IUI: 623	12.2	IUI: 7.4	56 509	34 445
	3350	FSH/IUI: 931	12.2	FSH/IUI: 8.7	69 316	42 251
Per couple	10 397	IUI: 2449	37.9	IUI: 29.1	89 694	54 673
	10397	FSH/IUI 3888	37.9	FSH/IUI: 36.5	445 635	271 636

[a]Incremental cost is the additional cost per IVF birth over the alternative IUI or FSH/IUI (Goverde *et al.*, 2000).
IUI = intrauterine insemination; NLG = Netherlands guilders; USD = US dollars.

Modelling approaches to cost-effectiveness

Models of cost and effectiveness associated with modifications of IVF procedures and medications are more common than RCT-based cost-effectiveness studies. In the absence of sufficient data from an RCT, existing observational and administrative data together with any RCT data that can be found, may be formed into a model of effectiveness to which cost data are applied. Modelling necessarily involves assumptions and judgements so that care must be taken to retain objectivity. Two recent publications made use of Markov models to address the cost-effectiveness of gonadotrophin treatments: both utilized expert panels to ensure objectivity, but took different approaches to account for uncertainty (Daya *et al.*, 2001; Sykes *et al.*, 2001). When data are drawn from different sources, customary methods of expressing uncertainty such as standard errors and confidence limits may not apply (Briggs, 1999; Briggs *et al.*, 1999). One study made use of sensitivity analyses to allow for variability in the assumptions about trends (Sykes *et al.*, 2001). The other utilized Monte Carlo simulation to establish confidence limits around the outcome estimates of interest (Daya *et al.*, 2001). In both studies, recombinant FSH was associated with a lower cost-effectiveness ratio than urine-derived FSH.

Models also have been developed to evaluate the broader issue of whether IVF is more cost-effective than other infertility treatments, and these are more prevalent than RCT-based publications. IVF was the most cost-effective treatment in severe tubal disease and severe endometriosis in a model based on effectiveness data from a systematic review, routine National Health Service data and UK public and private costs; other treatment protocols were more cost-effective for infertility associated with ovulation disorders, moderate male factors or unexplained infertility (Philips *et al.*, 2000). Another model incorporated published data on prognostic factors, live birth rates without treatment, live birth rates after IVF treatment, IVF cycle costs and the cost of associated twin deliveries (Callahan *et al.*, 1994; Mol *et al.*, 2000). The model compared four treatment policies: no treatment at all; three IVF cycles without delay; and either three or four IVF cycles if no treatment occurred within 30 months. If the female partner was aged over 35 years, immediate IVF was more cost-effective than a 30-month delay, even when the infertility was unexplained and of less than 2 years duration.

Three RCT-based cost-effectiveness analyses of IVF treatment have not resolved whether IVF is more cost-effective than standard therapy, and modelling depends on assumptions, even when a systematic review provides the effectiveness inputs. Despite the problems with RCTs, trials of the cost-effectiveness of IVF are needed to convince health policymakers that IVF treatment should be included in private and public insurance plans (Giacomini *et al.*, 2000). RCTs to evaluate the cost-effectiveness of IVF are challenging to design, expensive to conduct, and difficult to analyse. The trial interventions should reflect current clinical practice protocols and take place in typical clinical settings. IVF appears to be very effective, as indicated by registry results (Human Fertilisation and Embryology Authority, 2000; Centers for Disease Control, 2001). Therefore the required sample size and duration of follow-up should not be a barrier to the timely completion of IVF cost-effectiveness trials.

Table V. Comparison of incremental cost-effectiveness ratios

RCT interventions	Incremental cost-effectiveness ratio (US$; 2002)
IVF cycle versus 6 months' standard therapy (Karande *et al.*, 1999)	–26 586
IVF cycle versus 6 months' standard therapy (Soliman *et al.*, 1995)	79 472
IVF (3 cycles) versus IUI or FSH/IUI (4 cycles) (Goverde *et al.*, 2000)	47 749

IUI = intrauterine insemination; RCT = randomized, controlled trial.

Other types of economic analysis

Two additional types of full economic evaluations are cost-utility analysis and cost–benefit analysis. Unlike cost-effectiveness studies, these methods employ an effect measure that is common to all diseases and interventions. Cost-utility analyses consider the cost per quality-adjusted life year gained (QALY), or disability-adjusted life year gained (DALY) (Ganiats *et al.*, 1996). Because all outcome measures are converted to a common unit (QALYs gained), utility analysis results are comparable for diseases that involve mortality and/or morbidity. As the utility measures have this common basis, diverse healthcare interventions can be compared (Torgerson and Raftery, 1999). Despite this near-universal comparability, cost-utility analysis has little relevance to the management of infertility where lives are produced and not saved, and disability has been difficult to characterize and measure.

Cost–benefit analyses consider the cost per increment of comprehensive benefit measured in monetary terms such as dollars, euros or yen. In theory, the use of a common outcome means that the results of cost–benefit analyses would be comparable over a range of diseases and treatments, but it is difficult to convert mortality and morbidity into bleak monetary terms (Palmer *et al.*, 1999). Thus, cost–benefit analyses tend to address a narrow range of conditions—primarily those where a disease or its treatment brings about economic changes, such as the productivity of patients.

The 'willingness to pay' approach attempts to overcome these shortcomings of cost–benefit analysis. Estimating willingness to pay allows a simultaneous assessment of the value of primary outcomes, secondary outcomes, non-health benefits, and health process issues. Willingness to pay studies ask patients or members of the public how much they would be willing to pay for a given procedure, and the procedure with the highest value is the preferred choice (Gafni, 1991). The technique is most useful when issues such as cost and adverse effects are interwoven with benefit, as with IVF treatment. In one such study, 55% of infertile couples were willing to pay £10 000 for an IVF treatment pregnancy where the estimated direct costs per delivery were £9410 (Granberg *et al.*, 1995). Members of the general public in Massachusetts would have been willing to pay $32 per year for a public insurance programme that would provide 200 IVF cycles per million population per year (Neumann and Johannesson, 1994). At the same time, insurance for 300 cycles per million was estimated to cost $9.41 per full-time employee (Collins *et al.*, 1995).

Conjoint analysis is a procedure which can be used in any type of economic analysis using cost inputs and clinical data to estimate the value of the separate elements of a given service (Ryan, 1999). Conjoint analysis could, for example, evaluate access to the health service, waiting time, service delivery, important non-health outcomes and conventional health outcomes. In one conjoint analysis, IVF patients were asked for their input with respect to the chance of live birth, follow-up support, time on the waiting list, continuity of staff, attitudes of staff and cost. Surprisingly, patients seemed willing to make trade-offs between the probability of a live birth and other attributes of the IVF service. For example, good staff attitudes were more important than a 6% increase in the probability of live birth, but a 1% increase in live birth was seen as more beneficial than a 1-month reduction in time on the waiting list (Ryan, 1999).

Cost of IVF and ICSI multiple births

Numbers of multiple births, especially triplet and higher-order multiples, have increased since 1970 in countries where ovarian stimulation is used with infertility treatments such as IUI and IVF or ICSI cycles (Wheeler *et al.*, 1998). In the USA during 1980 to 1997, ovulation-inducing drugs and IVF treatment techniques each accounted for approximately 40% of the triplet and higher-order multiple births, the remainder having a natural origin (Division of Reproductive Health, 2000). In the 1998 IVF registry data, multiple births accounted for 30% of IVF-associated live births in the UK (Human Fertilisation and Embryology Authority, 2000) and 38% in the USA (Centers for Disease Control, 2001). Among live births, 3 and 6% were triplets or higher in the UK and USA respectively. In a Boston hospital, IVF treatment accounted for 2% of the singletons, 35% of the twins, and 77% of the high-order multiples (Callahan *et al.*, 1994), whilst in Alberta, IVF treatment accounted for 21% of the twins and all of the triplets born in the province from 1994 to 1996 (Tough *et al.*, 2000). Multiple birth can be a rewarding fulfilment of the wish to reproduce, but even twins have higher prematurity and perinatal mortality rates, creating psychological, medical, social and financial problems which are further magnified with higher-order pregnancies (Scholz *et al.*, 1999).

Cost studies indicate the burden of illness associated with multiple birth (Division of Reproductive Health, 2000). The average hospital costs for newborn babies reflect prematurity and perinatal morbidity and predict the future social, educational and medical costs of multiple birth that accrue during infancy and childhood. In the Boston study, the 1991 hospital costs per family were US$9845, $37 945 and $109 765 for singleton, twin and triplet births respectively (Callahan *et al.*, 1994). The rising costs associated with IVF multiple births in the USA began to exceed the costs of IVF procedures in 1998, based on the Boston study costs of multiple birth and USA IVF costs adjusted for inflation. By 2001, if the upward trend in triplet births in the USA has continued, the projected hospital costs of IVF-associated multiple births will be 60% higher than the costs of the IVF cycles (Collins and Graves, 2000).

IVF and ICSI costs, infertility treatment costs and national healthcare costs

Individual couples should consider not only the cost of a given treatment but also its usefulness in achieving the goal of infertility treatment, which is the birth of a healthy infant. The final decision, however, often depends on their ability to pay. Looking beyond individual patients, health policy decisions about funding infertility services should take into account the cost of IVF and ICSI services relative to the cost of other infertility treatments and their place in national health expenditures. This section reviews IVF and ICSI costs in the broader context of the cost of infertility diagnosis and treatment, family expenditures on health and national healthcare costs.

Costs of IVF and ICSI and overall management of infertility

Few studies address the overall cost of infertility management including both diagnosis and treatment. In the Illinois RCT, the treatment costs for standard management over 22 months were US$9557 per couple within the trial, and $9062 in the patients treated at the same time outside of the trial (Karande *et al.*, 1999). A Markov model of cost and cost-effectiveness in the UK included 16 diagnosis and treatment categories; IVF treatment was superior to surgery for severe tubal infertility, but FSH/IUI dominated IVF for unexplained infertility. The model did not incorporate volume of services however (Philips *et al.*, 2000).

Another model estimated the overall cost of infertility management, including diagnosis, in the cohort of infertile couples seeking treatment within one year (Collins *et al.*, 1997). In 1995, there were approximately 330 000 couples with infertility

Table VI. Infertility treatment model: 100 couples in Canada, 2002

Diagnostic group	Treatment	No. of couples	No. of cycles per treatment	Live birth rate per treatment (%)	Live births per 100 couples	2002 costs ($)	
						Per treatment	Annual
All diagnoses	Self-treated	40	12	14	5.6	23	11 753
Ovulation defect	Clomiphene	10	6	34.2	3.4	40	2571
	FSH	4	3	42.6	1.7	1665	21 280
Unexplained infertility	Clomiphene	10	6	27	2.7	40	2571
	IUI	5	5	20	1.0	354	9429
Endometriosis	Ovulation suppression	1	6	25	0.3	345	2204
	Surgery	2	-	25	0.5	4897	9794
Tubal factor	Surgery	4	-	21	0.8	4897	19 588
Male factor	IUI	5	5	14	0.7	354	9429
	DI	8	5	65	5.2	692	29 477
	Other	1	3	16	0.2	1555	1555
Persistent infertility	FSH + IUI	8	3	22.2	1.8	2207	56 405
	IVF/ICSI	2	1.7	36.8	0.8	7568	29 354
Totals		100		24.6			205 410

DI = donor insemination; IUI = intrauterine insemination.

in Canada, of which 150 000 were assumed to seek medical advice or treatment (Wilcox and Mosher, 1993). The distribution of treatment was based on published estimates (Collins *et al.*, 1993; Wilcox and Mosher, 1993). Thirteen diagnostic and treatment categories accounted for virtually all of the treatments received. In the model, after a year of treatment, 26% of the couples would achieve a live birth, based on then-current estimates of treatment effectiveness (ESHRE Capri Workshop Group, 1996). The annual costs (in CA$) of diagnosis and treatment per 100 couples were $77 000 and $200 000 respectively, totalling $277 000—an average of $2770 per couple. The cost per live birth ranged from $650 for clomiphene treatment of unexplained infertility to $41 000 for IVF. The latter treatment was utilized by 6% of couples; these couples would have 5% of the live births at 21% of the overall cost of infertility treatment. In contrast, 8% of couples having donor insemination treatment would have 20% of the births at 8% of the overall cost (Collins *et al.*, 1997).

Table VI shows an update of the 1995 model projected to 2002 with recent estimates of volume of service, effectiveness and cost estimates (Chaplin and Earl, 2000). For Canada, the best estimate of the number of infertile couples that actually receive healthcare for the problem is based on an American survey in which 2.3% of the female population aged 15 to 44 years obtained any kind of health services for infertility (Wilcox and Mosher, 1993). The female population of Canada aged 15 to 44 years in 2002 will number 6.87 million; 2.3% of this number is approximately 159 000, or 46% of the total of 350 000 couples with infertility. The most significant change in the 2002 model is the number of couples having IVF/ICSI cycles; the 6% 1995 estimate had been based mainly on the Canadian Infertility Treatment Evaluation Study (CITES) in the 1995 model (Collins *et al.*, 1993). In an October 2001 press release, the Canadian Fertility and Andrology Society indicated that there were 4292 IVF/ICSI cycles in 18 of 24 reporting clinics during 1999, and 4685 cycles in 19 of 23 cycles in 2000. These data are consistent with 5800 cycles of IVF/ICSI treatment in all centres in 2002. The average couple undergoes 1.7 cycles per annum, indicating that 3412 couples, or 2% of the 159 000 couples that seek treatment for infertility, would have IVF/ICSI treatment.

In Table VI, the live birth rate per treatment is live birth rate for the number of cycles or duration of treatment (the live birth rate per treatment should be multiplied by the number of couples to obtain the number of live births per 100 couples). The 2002 cost per treatment is the cost per cycle or month times the number of cycles or duration of treatment plus 6.5%, which was the proportion of couples having two treatments within one year in the CITES data. In the surgery and other treatment rows, cost is a one-time cost and duration for conceptions leading to live birth is the one-year interval after the procedure.

The estimated average cost of treatment for 100 couples was $205 410, or $2054 per couple in 2002. As in the 1995 model, treatment for persistent infertility is the most costly category. The total costs of FSH with IUI treatment (utilized by 8% of couples for three cycles) are more than the total costs of IVF/ICSI treatment (utilized by 2% of couples for an average of 1.7 cycles). IVF and ICSI treatment yields 3% of the live births among infertile couples, at 14% of the overall cost of infertility treatment. The model does not include the downstream costs of multiple births.

The 1995 annual cost of infertility management in Canada was estimated to be CA$415 million, which was 0.6% of the national public and private expenditures on healthcare that year. In 2002, the estimated total cost of diagnosis and treatment for infertility in 2002 would be approximately $437 million, which is 0.42% of the projected $104.4 billion 2002 spending on health (Statistics Canada, 2001). One reason for the small increase in overall expenditure for infertility services (5.3% in 7 years) is the much lower utilization of IVF in the 2002 model (2% compared with 6% in the 1995 model). The 1995 cost of all IVF and ICSI services, excluding multiple births, was $108 million, compared with $44 million in 2002. The per capita cost of infertility and IVF/ICSI services in 2002 would be approximately US$15.00 and $1.50 respectively, and both would be slightly higher if multiple birth costs were included.

Context of IVF and ICSI cycle costs for infertile couples

From the Canadian model, the per capita cost of IVF/ICSI services in 2002 would be approximately US$1.00. Whilst the total cost of IVF and ICSI services expressed per capita is extremely small, distributing the cost of IVF and ICSI treatment across a population in this manner is unrealistic, because in the majority of countries it is the infertile couples themselves who must pay for the treatment. It is therefore sensible to evaluate the relationship between IVF/ICSI cycle costs and family expenditures.

In Canada, average household expenditures (CA$) were $40 397 in 1998, on items including health ($1527), tobacco and alcohol ($1214), personal care ($693), education ($679), reading materials ($276) and games of chance ($249) (Chaplin and Earl, 2000). If projected to 2002, and based on 1995 to 1998 trends, the average total household expenditure would be $51 777. Thus, the $7568 cost of an IVF/ICSI cycle in 2002 would be approximately 15% of annual household expenditures. For the average couple having 1.7 IVF/ICSI cycles, the cost would be 25% of annual household expenditures.

IVF cycle cost appears to be an important fraction of annual family expenditures in many IVF-reporting countries besides Canada. In the UK, annual family expenditures in 2000–2001 were £20 072, including housing (£3323), motoring (£2865) and clothing (£2839) (www.statistics.gov.uk). The 2001 cost of a single IVF cycle would be £1988, which is 10% of total household expenditure (Philips *et al.*, 2000). Annual income or expenditure by families is not reported for many other countries, but gross national income (GNI) per capita is approximately 50% of average household income in western countries (Chaplin and Earl, 2000). GNI per capita for 1999 has been listed by the World Bank for 23 of the 26 countries for which IVF costs are known (www.worldbank.org/data/databytopic/GNPPC.pdf).

The cost of a single IVF cycle was greater than 50% of GNI per capita in 10 of 23 countries: China, India, Indonesia, Iran, Jordan, Lebanon, Malaysia, Pakistan, Saudi Arabia and Thailand. In the six Western European countries for which data were available (Denmark, Finland, the Netherlands, Norway, Sweden and the UK), the average 1999 cost of a single IVF cycle was US$2859, more than 10% of the $27 622 average 1999 GNI per capita. The 1999 cost of a single IVF cycle in the United States ($8039), is 25% of the 1999 GNI per capita ($31 910).

Comment

The high cost of treatment is the most salient health economic characteristic of IVF/ICSI therapy. Infertility which is persistent after conventional management is difficult to treat, and IVF/ISCI is as effective as many interventions for other late-stage or difficult-to-treat disorders. Nevertheless, fewer than 20% of those who need IVF/ICSI treatment actually utilize it; in 48 countries the average utilization was 289 c.p.m. pa, compared with the estimated need for 1500 c.p.m. pa. Lack of utilization is due in part to lack of availability: 21 countries have less than one IVF centre per million population. Generally, countries with few IVF centres rightly continue to place a higher priority on reducing high infant mortality rates. In the remaining countries, low utilization appears to reflect the high cost of IVF cycles, which would deplete a significant proportion of annual family income. Unfortunately, IVF and ICSI treatment is beyond the means of many infertile couples, limiting access to more affluent couples.

The high levels of price elasticity suggest that a 10% decrease in cost would generate a 30% increase in utilization. Some existing protocols (natural cycle IVF and single embryo transfer with subsequent cryopreservation cycles) and investigational methods (in-vitro oocyte maturation) have the potential to achieve such cost reductions and thereby to increase IVF/ICSI utilization. The goal of a five-fold increase in utilization to an international average around 1500 cycles per million population per annum remains somewhat more distant.

Descriptive studies of cost and cost-outcome studies make up the majority of the medical care research literature on the health economics of IVF and ICSI. The results of such studies contribute to background understanding, national cost summaries and international comparisons. What is needed for decisions on the allocation of funding, however, is the better quality evidence that comes from RCTs. Unfortunately, only three such trials formally compared IVF and/or ICSI with standard infertility treatment or no treatment (Goeree *et al.*, 1993; Karande *et al.*, 1999; Goverde *et al.*, 2000). The value of the existing evidence from RCTs is diminished because in each case the alternative intervention failed to reflect the actual options that are available to couples at the time they make decisions about IVF and ICSI. For a cost-effectiveness RCT to generate valid results that will have broad relevance, the control arm should be a significant two- to three-cycle delay in IVF/ICSI treatment, as a surrogate for placebo therapy. Delaying IVF treatment creates planning difficulties, whether in public or private settings, but the sample size for delayed treatment trials is more practicable. If the clinical setting demands an active control group to ensure participation, the sample size will necessarily be larger. Also, the alternative treatment should come from the narrow range of interventions that truly compete with IVF/ICSI. Acquiring cost data during the trial is time-consuming, but actual direct and indirect costs and facility costs should be determined from the various sources. The clinically relevant primary outcome is the incremental cost per singleton live birth. Meaningful secondary outcomes such as multiple births and adverse events should also be captured, because they can help to generate information on which to base planning for subsequent RCTs.

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