The cost effectiveness of intracytoplasmic sperm injection (ICSI)

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Abstract

Purpose To estimate the incremental cost effectiveness of ICSI, and total costs for the population of Australia.

Methods Treatment effects for three patient groups were drawn from a published systematic review and meta-analysis of trials comparing fertilisation outcomes for ICSI. Incremental costs derived from resource-based costing of ICSI and existing practice comparators for each patient group.

Results Incremental cost per live birth for patients unsuited to IVF is estimated between A\$8,500 and 13,400. For the subnormal semen indication, cost per live birth could be as low as A\$3,600, but in the worst case scenario, there would just be additional incremental costs of A\$600 per procedure. Multiplying out the additional costs of ICSI over the relevant target populations in Australia gives potential total financial implications of over A\$31 million per annum.

Conclusion While there are additional benefits from ICSI procedure, particularly for those with subnormal sperm, the additional cost for the health care system is substantial.

Keywords Health technology assessment · Cost-effectiveness · ICSI · IVF · Surgical sperm collection

Introduction

Intracytoplasmic sperm injection (ICSI) is an assisted reproduction technique which involves injecting a single sperm into the cytoplasm of an oocyte. The aim of ICSI is to provide additional treatment options for couples who could not be helped by conventional in vitro fertilisation (IVF). ICSI is used mainly in patients with low sperm concentration (<2 million/ml), low sperm motility (<5%), increased abnormal morphology (>95%), sperm autoimmunity, defective sperm-oocyte interaction and, in patients with obstructive azoospermia, using sperm or elongated spermatids collected from the male genital tract. ICSI is also used in couples where there has been previous low or zero fertilisation with standard IVF [1, 2].

ICSI can be conducted using both ejaculated and surgically retrieved sperm. Five per cent of Australian males are affected by infertility, and this is responsible for 40% of couples who seek assisted reproduction techniques [3]. Previously, fathering a child was virtually impossible for patients with untreatable azoospermia or other severe sperm abnormalities, options being limited to artificial insemination using donor sperm, adoption or ultimately remaining childless. The introduction of ICSI provides the possibility of having a child that is genetically linked to both parents [1, 2].

ICSI is an extensive service not usually subsidized by public funding, and so the scope for increased costs across society is substantial. It is important, and timely, that the costs and effects of introducing such a service are assessed. This paper reports an economic evaluation of ICSI services in Australia, including the potential costs for expansion of these services. Findings from this study have recently informed an independent review of public funding for assisted reproductive technology in Australia [4].

Capsule ICSI appears highly cost-effective for some categories of patient but may increase costs and provide no additional benefits for other indications.

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Methods

We use the standard cost effectiveness framework for the economic evaluation of a medical technology [5, 6]. This paper adopts a health system perspective and estimates the total and incremental (i.e. those over and above a comparator service) direct costs to patients and the health care system and effects of assisted reproduction that involves ICSI with and without surgical sperm collection. It makes use of original data from Australia, and costs are presented in Australian dollars (A\$). Little work has been undertaken internationally on the cost effectiveness of ICSI, especially with regard to the cost effectiveness of ICSI using ejaculated as opposed to surgically extracted sperm. A short summary of the literature can be found in Table 1.

ICSI is an extensive service in Australia, there are expected to be around 8,000 ICSI cycles per year [1, 2], with not a great deal of variation in this over time. Around 10–15% of ICSI cycles involve the surgical retrieval of sperm. There are obvious concerns about the potential costs, and associated effectiveness of such a service, particularly where public funding is involved. We report here an initial cost effectiveness analysis of this service, assessing the additional costs and live births compared with current services for two patient groups—ICSI with surgical sperm collection for obstructive azoospermia, and ICSI with ejaculated sperm for severe male factor infertility or for patients unsuited to IVF. This will provide new information to policy makers both in Australia and other similar health systems that offer such services.

Base case data

Based on private patient fees at two Australian IVF clinics, the 2003 per cycle cost for standard IVF is estimated at between A\$1700 for natural or clomid IVF and at upwards of A\$2,500 for stimulated IVF [1, 2]. Based on resource-based costing, an ICSI cycle without surgical sperm retrieval is estimated to cost an additional A\$624.29 in laboratory costs comprising procedure costs of A\$240 per cycle, eight hours of embryologist labour per cycle at A\$30/h, disposable costs of A\$82.61 per cycle and capital costs of A\$61.68 per cycle [1, 2]. This is in line with estimates based on private patient fees with ICSI attracting additional charges of up to A\$580 [1, 2].

Results

Based on the above figures, we assume a cost per cycle in 2003 for assisted reproduction that involves ICSI with ejaculated sperm of between A\$2,200 and 3,500—an

estimate not far removed from those in the literature reviewed (see Table 1), although the literature would suggest a figure towards the higher end of this estimate.

As regards the additional cost of surgical sperm retrieval, the respective costs of the percutaneous procedures (for example PESA and TESA) are not likely to be significantly different from each other, and the procedure will usually take place in an outpatient setting. Open biopsies (and sometimes TESE) are likely to be somewhat more expensive since they require a general anaesthetic and would be carried out in an operating theatre. It was not possible to place an exact cost on each of these procedures, but a standard open biopsy is likely to be similar to a biopsy of deep tissue or an organ which has an Australian Medical Benefits Schedule (MBS) cost (plus laboratory costs) of A\$367.¹ To this must be added the cost of the anaesthetist at A\$200, and theatre time (A\$338–677 depending if undertaken as private or public procedures). This gives costs of between A\$905 and 1,244. Including ICSI laboratory costs (A\$624), and A\$430 for micro dissection, this brings additional costs (over and above the cost of a standard IVF cycle) to between A\$1,959 and 2,298.

Multisite small incision and microdissection TESE procedures for severe primary spermatogenic disorders are more like microsurgical vasovasostomy or vasoepididymostomy in time and skill (MBS cost A\$547). With theatre costs (A\$338–677), and when combined with a laboratory cost for ICSI of A\$624 this would suggest a total cost (with A\$430 for microdissection) per case for sperm collection and ICSI of between A\$1,939 and 2,278. Some patients may undergo as many as eight treatment cycles before achieving a viable pregnancy, but the usual number is about four to five cycles [1, 2]. It is estimated that around half of treatments may involve a frozen embryo, this would add A\$500 on average (\$1,000 by 0.5) [1, 2]. Based on these figures and the cost per cycle of standard IVF given above, we assume a cost per cycle for assisted reproduction that involves ICSI and surgical sperm collection of A\$3,500–5,000, again an estimate not far removed from those in the literature reviewed (see Table 1), although again the literature would suggest a figure towards the higher end of this estimate.

For the subnormal semen indication, the absolute risk of at least one live birth per cycle under ICSI is estimated at between 0.10 and 0.27 [1, 2]. This estimate is based on an absolute risk equal to 0.105 of at least one live birth per cycle for couples with male factor subfertility under standard IVF [18] and on upper (2.57) and lower (0.98)

¹ The Australian Medical Benefits Schedule fees are the basis of the public subsidy for medical services based on an estimate of the cost of the service. The actual fee charged may be in excess of that level.

Table 1 Literature summary

Authors	Intervention	Costs	Cost-effectiveness
Granberg et al. [7]	ICSI with IVF compared to donor insemination for 715 couples having 901 ICSI treatments, and for 608 couples having 1,949 donor inseminations, using 1993 and 1994 direct and indirect costs	ICSI is estimated as costing SEK34,200 ^a –37,800 (A\$6,156–6,804)	With delivery as the outcome, estimated at 16% in 1993 and 24% in 1994 for ICSI, and 9% for donor insemination. ICSI direct cost per delivery was SEK284,400 (A\$51,192) in 1993 and SEK159,900 (A\$28,782) in 1994. Direct and indirect costs per delivery for ICSI were SEK264,300 (A\$47,574) in 1993, and SEK174,900 (A\$31,482) in 1994. Donor insemination cost SEK88,900 (A\$16,002) per delivery. Earlier work claims the cost of IVF without ICSI is SEK115,000 (A\$20,700) per delivery
Van Voorhis et al. [8]	Cost of ICSI with IVF, in the context of effect of total motile sperm count on intrauterine insemination (IUI), and IVF	—	With deliveries per cycle at 32.3%, cost per delivery for IVF with ICSI is US \$32,869 ^b (A\$57,192), compared to US \$22,248–57,997 (A\$38,712–100,915) for IUI
Philips et al. [9]	Male infertility comparing ICSI and SIUI (stimulated intrauterine insemination) with IVF	ICSI costs estimated at £2,562 ^c to 5,075 (A\$6,507 to 12,890)	Pregnancy rates are higher with ICSI, 9.3 per cycle, compared to 7.2 with SIUI. With ICSI average cost per pregnancy is estimated to be £9,229–8,273 (A\$23,442–21,013) (for one to four cycles respectively), compared to £4,362 (A\$11,079) for SIUI
Comhaire [10]	Male subfertility treatment ICSI with IVF	Estimated costs: BEF125,000 ^d (A\$5,000)	With a 55% success rate in the first two attempts, ICSI and IVF is estimated to cost BEF360,000 (A\$14,400) per delivery. For regular IVF (three attempts) costs are estimated at BEF550,000 (A\$22,000) per delivery
Ola et al. [11]	Estimates from the UK while discussing if ICSI should be the treatment of choice for all cases of in-vitro conception	ICSI is reported as more expensive, with a cost difference of £600 (A\$1,524) per fresh cycle completed	With data from 1998 and 1999 they report live birth rates per fresh treatment cycle for ICSI of 22.6%, which are significantly higher than those for IVF (21.6%, $p=0.01$). The incremental cost effectiveness is estimated at £60,000 (A\$152,400; $0.01 \times £600$) to gain one additional live birth when ICSI is advocated for all patients requiring IVF
Collins [12]	An international survey of the health economics of IVF and ICSI	Found the average cost of IVF/ICSI cycle in 2002 to be US\$9,547 (A\$16,612) in the USA, and US\$3,518 (A\$6,121) in 25 other countries (not including Australia)	Cost effectiveness is reported at US \$58,394 (A\$1,605) per live birth in the USA, and US\$22,048 (A\$38,363) elsewhere
Kolettis and Thomas [13]	Compares vasoepididymostomy for vasectomy reversal to microsurgical epididymal sperm aspiration and ICSI for treatment of epididymal obstruction secondary to vasectomy for 55 men	Cost per cycle of ICSI was estimated at US\$7,000 (A\$12,180), and cost of microsurgical epididymal sperm aspiration was US\$3,213 (A\$5,591). Normal delivery costs were estimated at US\$6,430 (A\$11,188), and assisted reproduction leads to additional cost for twins of US\$20,000 (A\$34,800), triplets US\$200,000 (A\$348,000), and complications are estimated at between	Assuming 29% delivery rate for microsurgical epididymal sperm aspiration and ICSI, cost per newborn was US\$51,024 (A\$88,782), compared to US\$31,099 (A\$54,112) for vasoepididymostomy

Table 1 (continued)

Authors	Intervention	Costs	Cost-effectiveness
		US\$2,500 (A\$4,350) and US\$26,000 (A\$45,240) depending on severity	
Heidenreich et al. [14]	Compares microsurgical vasovasostomy (VVS) for obstructive azoospermia following vasectomy to microsurgical epididymal sperm aspiration (MESA)/testicular extraction of sperm (TESE) combined with ICSI in Germany	VVS is estimated to cost €2,461 ^f (A\$4,036), and ICSI €2,974 (A\$4,877). MESA/TESE costs €369 (A\$605)	The outcome is measured at four MESA/TESE for one delivery (pregnancy rate 24.5%). Overall costs are estimated at €12,829 (A\$21,040) per normal delivery following MESA/TESE and ICSI, compared to €2,793 (A\$4,581) for normal delivery following VVS
Pavlovich and Schlegel [15]	Look at options after vasectomy—initial microsurgical vasectomy reversal, compared to retrieved epididymal or testicular sperm	Microsurgical sperm aspiration charges are US\$3,000 (A\$5,520); percutaneous aspiration US\$1,000 (A\$1,740); and ICSI charges average US\$11,324 (A\$19,704) per cycle	Delivery rate for one cycle of sperm retrieval and ICSI was 31%. Cost per delivery with vasectomy reversal was estimated at US\$25,475 (A\$44,326; delivery rate 47%). Cost per delivery after sperm retrieval and ICSI was US\$72,521–73,146 (A\$126,187–127,274) with percutaneous or testicular retrieval and US\$71,896 (A\$125,099) for surgical epididymal sperm retrieval
Alfonsin et al. [16]	Look at gamete transport assisted reproduction in Argentina	Transport ICSI is estimated to cost US\$3,100 (A\$5,394) with conventional ICSI costing US\$4,500 (A\$7,830)	—
Deck and Becker [17]	Look at vasectomy reversal compared to IVF with ICSI	Estimate a cost of US\$8,135 (A\$14,155) for testicular sperm extraction and one cycle of IVF with ICSI	Cost per newborn of US\$3,940 (A\$180,856) for an 8% birth rate, compared to US\$28,530 (A\$49,642) per newborn for vasectomy reversal, if the ovulating partner is over 37 years old

^a 1 Swedish Kroner (SEK)=0.18 Australian Dollar (A\$)

^b 1 US Dollar (US\$)=1.74 Australian Dollar (A\$)

^c 1 UK Pound (£)=2.54 Australian Dollar (A\$)

^d 1 Belgian Franc (BEF)=0.04 Australian Dollar (A\$) (Prevailing exchange rate as currency now the EURO €)

^e 1 Euro (€)=1.64 Australian Dollars (A\$)

point estimates for the ICSI versus standard IVF relative risk of per cycle fertilisation from a systematic review of trials comparing fertilisation outcomes under ICSI and IVF without surgical sperm retrieval [1, 2]. If the live birth rate is 10% per ICSI cycle, at a cost of between A\$2,200 and 3,500 per cycle then the crude cost per birth for ICSI with ejaculated sperm, is approximately A\$22,000–35,000. Clearly if the live birth rate per cycle is higher the cost per live birth is proportionately reduced. At an upper-end estimate of 25% live birth per cycle of ICSI, the cost per live birth of ICSI without surgical sperm collection would be of the order of A\$8,800–14,000, see Table 2.

Undertaking the same analysis for ICSI with surgical sperm retrieval, if the birth rate is assumed to be 10% per ICSI cycle at a cost of between A\$3,500 and 5,000 per cycle then the crude cost per birth for ICSI, including aspiration procedures to retrieve sperm, is approximately A

\$35,000–50,000. Clearly, if the live birth rate per cycle is higher the cost per live birth is proportionately reduced. At a rate of 25% per cycle of ICSI, the cost per live birth of ICSI with surgical sperm collection would be of the order of A\$14,000–20,000, see Table 3.

Table 2 Sensitivity of cost per birth to birth rates (ejaculated sperm)

Birth rate (%)	Cost per birth, with costs at A\$2,200	Cost per birth, with costs at A\$3,500
10	A\$22,000	A\$35,000
15	A\$14,667	A\$23,333
20	A\$11,000	A\$17,500
25	A\$8,800	A\$14,000

Table 3 Sensitivity of cost per birth to birth rates (surgical sperm retrieval)

Birth rate (%)	Cost per birth, with costs at A\$3,500	Cost per birth, with costs at A\$5,000
10	A\$35,000	A\$50,000
15	A\$23,333	A\$33,333
20	A\$17,500	A\$25,000
25	A\$14,000	A\$20,000

Incremental cost effectiveness of ICSI with surgical sperm-retrieval

The alternative treatments to ICSI depend on the indication. The most common conditions managed by ICSI with sperm from the genital tract include bilateral congenital absence of the vas, epididymal or ejaculatory duct obstruction, and the largest single group, vasectomy-related infertility.

For azoospermia as a result of vasectomy, reversal by microsurgery is often possible, and in many cases may have better results than ICSI. The success rate in achieving a birth depends on a number of factors, but is often quoted as at least 50% by 1 year after the operation [1, 2]. If we assume that for an infertile couple, where the cause is a prior vasectomy, the success rate for vasectomy reversal is 50% compared to 10% for ICSI per cycle and the cost is A\$4,500 compared to A\$3,000 for ICSI, then the cost per extra live birth for vasectomy reversal compared to ICSI in this group would be A\$3,750.

In those indications where surgical or other treatments are not possible (or in cases of vasectomy where reversal is very unlikely to be successful), and donor insemination unacceptable, the additional cost per extra live birth is likely to be of the order of A\$30,000–40,000 as compared to no treatment [1, 2]. Where conditions such as gonadotrophin insufficiency or pituitary prolactinoma are amenable to drug therapy, ICSI may not be as cost effective as first line drug therapy with an estimated cost of A\$1,300.

These figures include the cost of hospital admission, drugs and the co-payment (*Transcript of evidence*, Dr John McBain, ProofHansard, p 173). Table 4 summarises overall cost and financial implications on the assumption that 10–15% of ICSI involves sperm aspiration.

Incremental cost effectiveness of ICSI with ejaculated sperm

For patients unsuited to standard IVF and who in the past may have been treated with partial zona dissection (PZD) or subzonal insertion of sperm (SUZI), the appropriate existing practice comparator for ICSI is no treatment. Kastrop et al. [19] found an absolute risk of at least one live birth per cycle equal to 0.261 in patients unsuited for standard IVF. These results are at the upper end of estimates for the subnormal semen indication and refer to a subset of patients meeting the unsuited for standard IVF indication (i.e. patients who have failed high insemination concentration-, or HIC-, IVF). If the birth rate is assumed to be 26.1% per ICSI cycle at a cost of between A\$2,200 and 3,500 per cycle, then the crude cost per birth for ICSI is approximately A\$8,500–13,400. Clearly if the birth rate per cycle is lower then the cost per birth is proportionately increased.

In patients for whom IVF offers any possibility of fertilisation (subnormal semen, failed IVF and mixed indications), the appropriate existing practice comparator for ICSI is standard IVF. For the subnormal semen indication, the absolute risk of live birth using ICSI is estimated at between 0.1029 and 0.27 per cycle, based on the best available evidence as to the relative risk of per cycle fertilisation and a baseline live birth rate under standard IVF of 0.105 per cycle [18]. At best, substituting ICSI for standard IVF in patients meeting the subnormal semen indication would increase the live birth rate by as much as 16.5%. At worst, substituting ICSI for standard IVF in patients meeting the subnormal semen indication would result in no additional benefit. The additional cost of substituting ICSI for standard IVF in patients meeting the subnormal semen indication was estimated at just over A

Table 4 Cost summary

	Total cost	Cost per birth	Financial implications per annum
Surgical extraction of sperm, ICSI, IVF	A\$3,500–5,000	A\$14,000–50,000	A\$2.8–6 million (10–15% of ICSI cycles)
ICSI and IVF with ejaculated sperm	A\$2,200–3,500	A\$8,800–35,000	A\$15–25.3 million
Total			A\$18–31 million

Table 5 Incremental cost effectiveness

	Incremental costs	Birth rate (%)	Incremental cost per birth
Patients unsuited for standard IVF	A\$2,200–3,500	26	A\$8,500–13,400
Subnormal semen indication	A\$600	16.5	A\$3,636–Dominated (no benefits, just additional costs)

\$600 (see above). As such, for the subnormal semen indication, each additional live birth would cost an extra A\$3,636 under the best case scenario. For the worst case scenario, ICSI would cost an extra A\$600 per cycle and would deliver no additional benefit. For the failed-IVF and mixed indications, it has not been possible to estimate the relative risk of a live birth based on per oocyte fertilisation rates or on per cycle fertilisation rates. Therefore, there is no basis on which to calculate incremental cost effectiveness. See Table 5 for a summary of incremental cost effectiveness.

Discussion and conclusion

The literature suggests that, compared to the option of vasectomy reversal (vasoepididymostomy or vasovasostomy), and repeat reversal, costs per live birth with ICSI are higher, by as much as a factor of three. ICSI also costs more per live birth than donor insemination (by a factor of almost two).

We estimate cost per cycle for assisted reproduction that involves ICSI without surgical sperm collection at A\$2,200–3,500, with the literature suggesting a figure towards the higher end of this estimate. This gives a per cycle cost per live birth of A\$8,800–35,000. This would seem a reasonable estimate given that the international literature all suggests additional costs for ICSI, when compared to other procedures. It should be noted these figures may be based on conservative estimates of birth rates derived from published trials, and that registry data suggests a trend towards higher rates.

Incremental cost per live birth for patients unsuited to standard IVF is estimated at between A\$8,500 and 13,400. For patients with subnormal semen indication cost per live birth could be A\$3,600, but if there are no benefits, as in the worst case scenario, there would just be additional incremental costs of A\$600 per procedure.

For those with no alternative means of reproduction (10–15% of ICSI), the additional annual cost of surgical sperm retrieval for the health care system would be A\$1.6 million to 2.8 million [1, 2] and the associated cost of ICSI would be in the range of A\$2.8 million to 6 million. This is in addition to costs of between A\$15 and 25 million for ICSI and IVF with ejaculated sperm, giving potential total financial implications of over A\$31 million per annum. These figures raise real opportunity implications for health care systems, given financial constraints.

We end by acknowledging that there are several areas of economic uncertainty here. For example, will numbers of

cycles remain steady? Will the pregnancy rate stay constant? What are the additional psychosocial benefits (over and above pregnancy) for infertile men amenable to treatment? What are the downstream costs in terms of inherited infertility? What are the downstream costs and benefits to society? It is only for certain categories of patient that ICSI will provide any benefit, although it is used internationally for other indications than male infertility. Otherwise there will just be additional costs, with no benefit. We recommend that future research address these questions.

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