

Acceptable cost for the patient and society

Georgina M. Chambers, Ph.D.,^a G. David Adamson, M.D.,^b and Marinus J. C. Eijkemans, Ph.D.^c

^a National Perinatal Epidemiology and Statistics Unit, School of Women's and Children's Health, University of New South Wales, Randwick Hospitals Campus, Sydney, New South Wales, Australia; ^b Fertility Physicians of Northern California, Palo Alto, Stanford University, Stanford, and University of California, San Francisco, San Francisco, California; and ^c Department of Biostatistics and Research Support, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Alongside the debate around clinical, scientific, and ethical aspects of assisted reproductive technology (ART), there exists a parallel debate around the economics of ART treatment and what is the most appropriate funding framework for providing safe, equitable, and cost-effective treatment. The cost of ART treatment from a patient perspective exhibits striking differences worldwide due to the costliness of underlying health care systems and the level of public and third-party subsidization. These relative cost differences affect not only who can afford to access ART treatment but how ART is practiced in terms of embryo transfer practices; in turn significantly impacting the health outcomes and costs of caring for ART conceived children. Although empirical evidence indicates that ART treatment is “good value money” from a societal and patient perspective, the challenge remains to communicate this to policy makers, primarily because fertility treatments are not easily accommodated by traditional health economic methods. Furthermore, with global demand for ART treatment likely to increase, it is important that future funding decisions are informed by what has been learned about how costs and economic incentives influence equity of access and clinical practice. In this review we provide an international perspective on the costs and consequences of ART and summarize key economic considerations from the perspective of ART patients, providers, and society as a whole in the coming decade. (*Fertil Steril*® 2013;100:319–27. ©2013 by American Society for Reproductive Medicine.)

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There is little doubt that the treatment of infertility has been revolutionized during the past generation with the evolution of assisted reproductive technologies (ART) into a suite of mainstream medical treatments. Although the science, clinical practice, and ethical considerations of ART have rightly taken center stage, there has been a parallel debate around the most appropriate means of providing and funding equitable, safe, and cost-effective ART treatment. Latest estimates indicate that more than 1.6 million ART cycles are undertaken

each year and that, worldwide, more than 5 million children have now been born following ART (1), including up to 5% of all children in some countries (2). Despite this, there are striking international differences in utilization of ART and embryo transfer (ET) practices, even among developed countries where the prevalence and causes of infertility are similar (3). The reasons for such disparities are multifactorial, and include the diversity of regulatory and funding environments, demographic differences, and the influence of sociocultural norms. However,

there is a growing body of evidence demonstrating how the cost of treatment, particularly from a patient’s perspective, provides an important explanation for differences in utilization rates and ET practices. Such differences have important ethical implications in terms of equity of access, safe clinical practice, and ultimately the health outcomes and future health care resource consumption by ART mothers and babies.

The uptake of ART has occurred during a period of rapid growth in health care expenditure, both in real terms and as a percentage of gross domestic product (GDP) worldwide (4). Health care spending as a percentage of GDP in Organisation for Economic Co-operation and Development (OECD) countries has risen by an unsustainable 22% during the past decade. On average OECD countries spend ~9.5% of GDP on health care, with the United States a standout, spending 17.6% of its

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Reprint requests: Georgina M. Chambers, Ph.D., National Perinatal Epidemiology and Statistics Unit, School of Women's and Children's Health, University of New South Wales (UNSW), Level 2, McNevin Dickson Building, Randwick Hospitals Campus, Sydney, NSW, Australia 2031 (E-mail: g.chambers@unsw.edu.au).

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GDP on health care (5). Rising health care costs have meant that cost containment and “value for money” in health care have become key concerns for the delivery of new technologies and services worldwide. The pressing need to make health spending more sustainable has been underscored by significant health care reform and the growing emphasis by both public and private payers for treatment to be not only clinically effective, but also cost-effective (6). Fertility treatments have not escaped this pressure, exemplified by this year’s update to the United Kingdom National Institute of Clinical Excellence (NICE) Fertility guidelines (7), and recent changes in public funding in Denmark, Australia, the Netherlands, and Canadian provinces (8–11).

In this review, we present a global perspective on the costs and consequences of ART from different payer perspectives. We describe recent estimates of the direct and indirect costs associated with ART treatment, review the evidence regarding how consumer costs influence access to treatment and clinical practice, and explore whether ART represents good value for money compared with other health care interventions. Finally, we summarize what we believe to be the key economic considerations for ART patients, providers, and society as a whole in the coming decade.

ART COSTS: WHICH COSTS AND FROM WHOSE PERSPECTIVE?

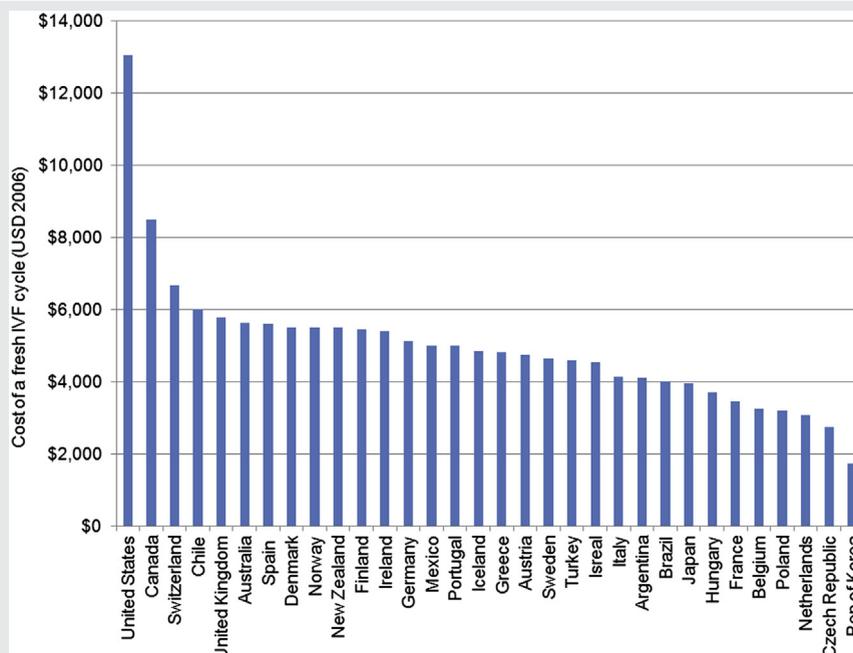
Costs associated with ART treatment are generally described as direct costs (those directly attributable to providing treatment) and indirect costs (those occurring as a consequence of ART treatment). Direct costs include resource

consumption due to medical consultations, hormones and medications, laboratory and embryology services, medical procedures, hospital charges, nursing and counseling services, and administrative and overhead charges. Indirect costs include the cost of treatment complications (e.g., ovarian hyperstimulation syndrome [OHSS]), patient travel costs, lost productivity, and most significantly, the downstream costs associated the caring for multiple birth infants. Although theoretically the correct cost of a resource is its opportunity cost (i.e., the value of foregone benefits), this is rarely quantifiable in imperfect markets, such as health care, where there are high levels of cross-subsidization, cost-aggregation, and market regulation. Therefore, the most pragmatic approach, and the one used in this review, is to use market charges as a proxy for costs, recognizing that the cost-to-charge ratio may vary among and even within countries. A societal viewpoint of costs considers all direct and indirect costs regardless of who incurs them, whereas consumer (patient) costs generally refer to the either direct or indirect net market charges.

Direct Costs of Treatment in Developed Countries

With these limitations in mind, a review of the direct unsubsidized costs of ART treatment across 32 middle and high income countries shows that the average cost of a single fresh in vitro fertilization (IVF) cycle is \$4,950 (USD), ranging from \$1,800–\$13,000 per cycle (Fig. 1). The cost of treatment tends to reflect the underlying costliness of a country’s health care system, for example, the United States has the most expensive health care system in the world in terms of health

FIGURE 1



Direct cost of a fresh IVF cycle before government of third-party subsidization 2006/2007. Purchasing power parity and average 2006 interbank exchange rates were used to convert all currencies to 2006 USA. Costs include pharmaceuticals.

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care expenditure per capita and total expenditure as a percentage of GDP and also has the most expensive ART treatment in the world (12).

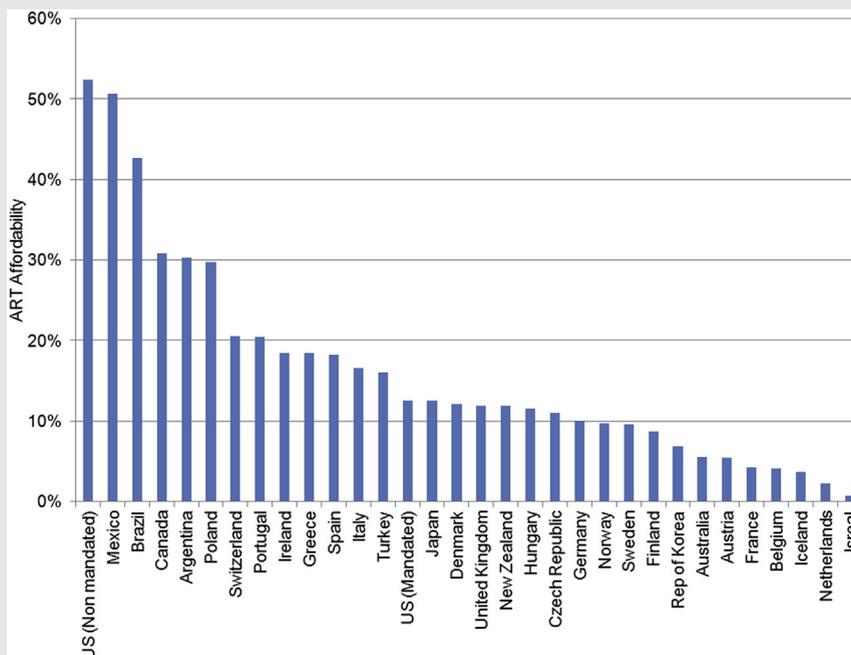
However, because of the considerable variation in funding arrangements for ARTs among and even within countries, the actual net cost to the consumer can be much reduced after subsidises. Public financing of ART ranges from virtually no subsidization in the United States and most developing countries, to complete funding of a limited number of cycles for eligible patients in most European countries, to unrestricted subsidization with copayments in Australia. The latest estimates from the International Federation of Fertility Societies (IFFS) Surveillance indicate that in 2010 64% of reporting countries offered some form of ART financing through national health services or third-party insurers. This compares to 46% of reporting countries in 2004 (13, 14). Although the United States has very limited public funding for ART, there are mandates in five states to offer ART treatment as part of employer-based insurance schemes (15).

The economic burden that ART treatment represents to a consumer (i.e., how affordable it is) is a function of the underlying cost of treatment, the level of public or third-party insurance to subsidize this cost, and the available income of consumers. When these three factors are combined for a particular country or jurisdiction, the relative affordability of ART from a patient's perspective can be compared. Using the direct treatment costs shown in Figure 1 and funding

arrangements in 2007/2008, a review of the affordability of ART treatment in each country reflects even more variation than in unsubsidized costs in terms of the economic burden of paying for treatment (Fig. 2). For example, in 2007/2008 the cost of a fresh IVF cycle represented 52% of average annual disposable income in US states without mandates compared to 13% of average annual disposable income in the five US states with mandates. This situation creates significant financial barriers to ART access for many United States citizens, particularly those in the 45 states without insurance mandates for ART, and in which there may be variable coverage between the extremes of mandated full coverage versus none. It should be noted that this cross-jurisdiction analysis represents a snapshot of ART consumer affordability at a particular time and because ARTs are susceptible to changes in funding policies, relative consumer affordability is also subject to variation over time.

From a societal perspective, the direct costs of treatment relate not only to the per cycle costs but also to the volume of treatments undertaken and what proportion of the total health care dollar this consumes. A review of six developed countries representing diverse funding and regulatory arrangements for ART found that in countries with supportive public funding, such as Australia and the Nordic countries, ART consumed around 0.25% of total health care expenditure, whereas ART treatment in the United States consumed around 0.06% of total health care expenditure (17), with great

FIGURE 2



Affordability of assisted reproductive technology (ART) treatment, 2006/2007. ART affordability is expressed as the net cost of a fresh IVF cycle as a percentage of annual disposable income of a single person earning 100% of average wages with no dependent children. Disposable income is calculated according to Organisation for Economic Co-operation and Development (OECD) methods (16). United States (Mandated) denotes data from a sample of three US states with comprehensive insurance mandates for ART (Connecticut, Massachusetts, New Jersey). United States (non-mandated) denotes data from a sample of three US states with no fertility treatment mandates (Michigan, Oregon, Washington).

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variability among the states. Therefore, it can be reasonably concluded that ART treatment is often expensive from a patient's perspective but not from a public or third-party insurance perspective. This observation is supported by a number of cost analyses of ART as part of medical insurance plans (18–20).

Costs in Developing Countries

Much of the global burden of infertility in terms of number of cases and psychosocial stigma is suffered by couples in resource-poor developing countries whose plight is worsened by a chronic lack of access to reproductive health care. However, infertility is not widely recognized as a priority in countries with overpopulation and health care systems struggling to provide basic health care needs (21–23). The incidence of infertility in resource-poor countries displays wide geographic variation, but is estimated to be similar to those in developed countries at around 9% of couples (3, 24, 25). However, the etiology of infertility in these countries differs from those in developed countries with higher rates of secondary infertility and tubal factor infertility resulting from sexually transmitted infections (STI) and postpartum infections (26).

The high rates of infertility and the causal relationships between STIs and reproductive health have been recognized by a number of international organizations and governments. In 2001, the World Health Organization recommended that infertility be considered a global health problem and recommended that public funding for ART be sought (27). Similarly, in 2005 at the United Nations' World Summit on Millennium Development Goals, world leaders committed to achieving universal access to reproductive health by 2015 (28). However, despite these declarations, very little progress has been made in education and reproductive health care in developing countries (29). A number of professional societies and not-for-profit foundations have been established in recent years to promote accessible and affordability fertility care in developed countries. These include the European Society of Human Reproduction and Embryology (ESHRE) Task Force on Developing Countries and Infertility (www.eshre.eu), the International Federation of Gynecology and Obstetrics Committee on Reproductive Medicine (www.figofertilitytoolbox.com), and the United States based charity Low-Cost IVF Foundation that aims to provide ART treatment for \$500 per cycle in developing countries (www.lowcost-ivf.ch, www.friendsofivf.org [30]).

Costs of Donor Eggs, Embryos, and Surrogacy

Due to the changing nature of family structures (e.g., single-parent and same-sex unions) and the trend to later child-bearing in many countries, the increasing demand for donor gametes and embryos is likely to continue. The degree of legislation and commercialization governing donor treatment is greatly influenced by sociocultural and religious norms. In countries that allow donations, several specifically prohibit financial compensation to the donor, including Australia, Canada, France, Greece, Korea, the Netherlands, and Vietnam, whereas other countries, such as Spain and the Czech Republic, allow some compensation. In contrast, the United States

allows payment for donor gametes (but not for embryos) leading to a growing, demand-driven market in that country (31, 32). The Ethics Committee of The American Society for Reproductive Medicine (ASRM) recommends that total payments to donors in excess of \$5,000 require justification and sums above \$10,000 are not appropriate (33).

In the United States egg and embryo donation continues to grow with almost 15,973 cycles of oocyte donation reported to the Society for Assisted Reproductive Technology (SART) registry in 2011, representing ~13% of all ART cycles in that year (34). Costs incurred by recipients are substantial, and a marked increase in price has occurred during the past 20 years. Current estimates for a donor IVF cycle are around three times higher than for an autologous cycle at \$30,000 (32).

The number and cost of surrogacy cycles are very difficult to quantify worldwide. Anecdotal estimates from the United States in 2008 have been put at ~1,400 babies per year and increasing, with costs ranging from \$40,000–\$120,000 (35).

Indirect Costs

Despite a long held recognition of the clinical risks to mothers and babies associated with ART multiple birth pregnancies, many countries persist in having very high iatrogenic multiple birth rates. Latest estimates put the ART multiple birth rate at 34% in the United States and 24% in the United Kingdom (36, 37). These compare with rates of less than 10% in Australia, Sweden, and Belgium, and multiple birth rates in the general population of 1–2%. In addition to the medical complications associated with multiple births, the resultant financial costs of caring for infants and mothers are substantial. A number of cost analyses have shown that the maternal and infant cost of a twin pregnancy during the perinatal period are approximately three times that of a singleton pregnancy (38–41). In addition, the cost of caring for multiple birth infants has been shown to extend beyond the perinatal period. For example, compared with normal birth weight children, low birth weight children with and without disabilities use more health care and educational resources to at least 8–9 years of age (42, 43).

The total burden placed on national health care systems from complications arising from ART multiple births is substantial. A recent cost analysis of preterm infants born in the United States as a result of ART multiple births estimated that the total health care cost was ~\$1 billion (USD) annually, which approximates the total direct cost of ART treatment in that country (44). Similarly, analyses of United Kingdom and Australia data have shown that the savings in caring for multiple birth infants has theoretically cross-subsidized much of the increase in ART utilization in those countries (40, 45).

HOW DO CONSUMERS RESPOND TO ECONOMIC INCENTIVES?

Differences in utilization rates and clinical practice among countries are multifactorial and reflect differences in regulatory and funding environments, sociocultural norms, access, and clinician autonomy. However, a growing body of

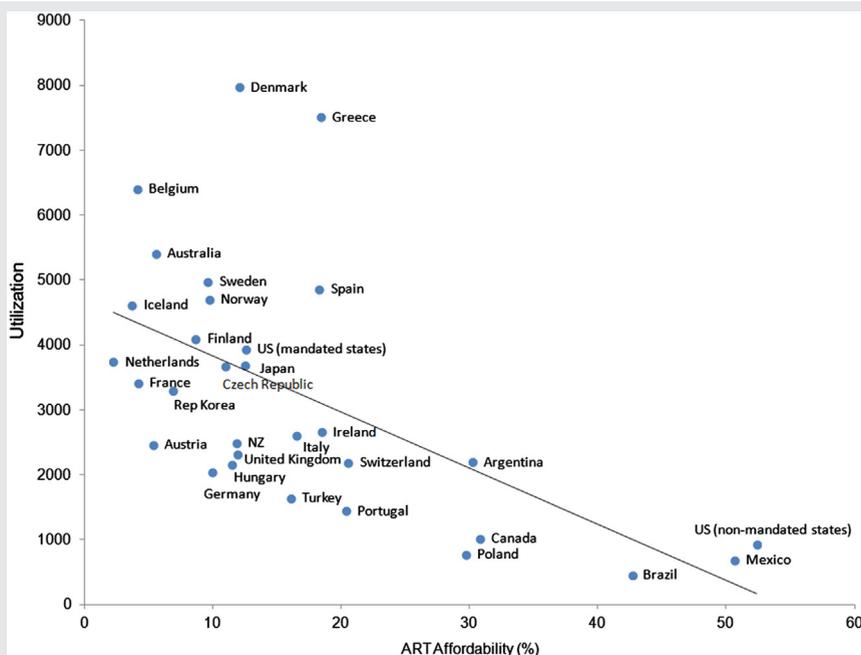
evidence is emerging on how the relative difference in affordability of ART treatment among countries impacts utilization rates and ET practices. One of the most notable disparities exists between the United States and Nordic countries. The Nordic countries are considered world leaders in ART, performing 2.5 times more ART cycles per woman of reproductive age than the United States and doing single ET in 56% of fresh embryo treatment cycles compared with 13% in the United States (2, 46). An obvious difference between these fertility markets is that ART treatment is more affordable in European countries than in the United States (Fig. 2). Plotting the affordability of ART treatment as presented in Figure 2 against the number of fresh cycles per million women of reproductive age clearly shows the correlation between consumer affordability and uptake of ART treatment among different countries (Fig. 3).

The measure of the responsiveness of demand to changes in cost is known as the price elasticity of demand and is often used by policy makers to predict how changes in consumer cost will impact consumer behavior and health care budgets. Few empirical analyses of the price elasticity for ARTs exist, but an analysis of data from Germany before and after the introduction of copayments for ART in 2004 suggests that a 10% price increase reduced utilization by 3%–4% (47). Similar estimates of ART price responsiveness were found based on an analysis of a 2010 policy that capped government payments for ARTs in Australia (10).

Although it is clear that more affordable treatment improves access, the behavior of consumers to lower consumer costs is not uniform. A number of studies have shown that certain ethnic groups and lower socioeconomic groups are less likely to access ART treatment even when access is improved through lower consumer costs (48–52). Furthermore, studies using United States data have found that patients who seek treatment in response to lower cost in mandated states may include those with better and poorer prognoses for ART treatment than those in non-mandated states (53, 54).

Treatment affordability has also been shown to influence the number of embryos transferred. Analysis of United States data has shown that states with comprehensive insurance mandates transfer lower average numbers of embryos than those with limited or no insurance mandates and that these differences cannot be fully explained by differences in patient population characteristics (53–56). In a bid to reduce ART multiple birth rates, a number of jurisdictions including Belgium, Turkey, New Zealand, and Quebec have made public funding contingent on clinical practice guidelines that dictate the number of embryos to be transferred (57–60). Such arrangements have dramatically reduced ART multiple birth rates but have also removed clinician and patient autonomy. In contrast, Australia is a prime example of a jurisdiction in which ET practices have not been directly tied to public funding, yet has achieved an

FIGURE 3



Assisted reproductive technology (ART) affordability and utilization, 2006/2007. ART Affordability is expressed as the net cost of a fresh IVF cycle as a percentage of annual disposable income of a single person earning 100% of average wages with no dependent children. Disposable income is calculated according to Organisation for Economic Co-operation and Development (OECD) methods (16). Utilization is expressed as the number of fresh autologous cycles per one million women of reproductive age (15–49 years).

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equivalently low ART multiple birth rate of ~8%; presumably with the assistance of a policy of supportive public funding that minimizes the incentive to achieve pregnancy at the expense of safe ET practices (61, 62).

ARE ARTs GOOD VALUE FOR MONEY?

Fertility treatments pose a challenge for health economists and policy makers alike in terms of informing decisions about whether they represent good value for money compared with other uses of health care resources. Fertility treatments are intrinsically different from other types of medical care because they are judged on their ability create new life rather than to extend or improve the quality of existing life, and therefore do not lend themselves to usual health economic methods.

Cost-effectiveness analysis, which measures the outcomes of alternate medical interventions in natural units (e.g., pregnancy rates, live birth rates), can easily accommodate the evaluation of competing fertility treatments and ET strategies. However, cost-utility analysis is the primary method used by governments and health technology assessment organizations to guide decisions about the allocation of public resources because it allows for the economic comparison of interventions that result in different health outcomes (e.g., fertility treatment, immunization, cancer treatment). Cost-utility analysis typically measures outcomes in quality adjusted life years (QALYs) and is therefore problematic for fertility treatment because QALYs are intended to capture improvements in health among living patients and, in theory, it is not possible to improve the health of someone who has not yet been conceived. However, the recent update to the United Kingdom NICE Fertility guidelines incorporated QALYs for women seeking fertility treatment in their economic evaluation of ART treatment. Acknowledging the limitations of such a modeling exercise, NICE concluded that under most clinically appropriate circumstances access to ART treatment and single ET represents good value for money from a societal perspective (7).

An alternative approach used to quantify the acceptability of ART treatment in economic terms is to use cost-benefit analysis in which outcomes are measured in purely financial terms. Falling into this category are a number of studies that have used investment evaluation techniques to quantify the return on government investment in ART treatment in terms of future net tax revenues during an ART child's lifetime. For example, using data from the United Kingdom, the discounted net tax revenue of an ART singleton child born in 2005 was found to be roughly \$208,400 (USD), representing an eight-fold return on investment for the government (63). Although forecasting the fiscal impact of ART conceived children using either a generational accounting or government budget framework is valid, demographic considerations and the value placed on increasing a nation's population will determine the desirability of investing in ART treatment. Also, it only represents a good investment for couples who would not have reasonably been expected to achieve a pregnancy without ART treatment.

Contingent evaluation techniques to elicit society's willingness to pay for ART treatments also fall into the

category of cost-benefit analysis. Although there is a lack of empirical evidence to validate whether these methods are applicable to fertility treatments, one pilot study did attempt to quantify ART treatment from an ex-post (user-based) perspective and ex-ante (insurance-based) perspective finding that the implied willingness to pay for a baby was \$177,730 for potential child bearers in the event that they were infertile, and \$1.8 million for society to pay for insurance to allow couples access to ART (64).

While it is doubtful that an unconceived life is valued in the same way as a life already being lived, it is informative to look to other sectors that value human life in economic terms such as the insurance industry and transportation safety agencies. Although health care is found to elicit lower valuations of human life than other sectors, the value of a statistical life is often quoted in the vicinity of \$1–\$6 million (65, 66). For example, the United States 9/11 government fund compensation estimates for victims are on average about \$2–\$3 million per life, with a range of \$0.25–\$7.1 million across all studies (67).

In summary, regardless of the approach taken to valuing ART treatment, the implied or explicit monetary value of providing ART treatment far exceeds the cost per child conceived, suggesting that ART treatment is indeed good value for money—particularly if ART children are born as singletons. Despite this it will be necessary to meet the challenge of demonstrating the value and cost-effectiveness of ART compared with other medical interventions to make ART less vulnerable to changes in public funding. However, given the strong sociocultural norms associated with ARTs, and the increasing use of ARTs to create non-traditional families, it is likely that other considerations, such as equity of access and the perceived role of ART in population growth, will play just as important a role in funding decisions as do traditional health economic methods.

Furthermore, there are many non-economic benefits of ART and although difficult to quantify, these benefits are not inconsequential. The popular discourse in the scientific and lay media around the topics of “happiness” and “a meaningful life” often include discussions about the role that parenthood plays in these life goals. The empirical research of whether parenting indeed increases levels of happiness is conflicting. However, the majority of people consider parenthood as a vital mode of fulfillment and there is near consensus that parenting provides for a satisfying and meaningful life (68, 69). A recent adaptation of Maslow's pyramid of human needs positioned parenting at the top of the pyramid to reflect its central role in human life (70).

FUTURE ECONOMIC CHALLENGES AND IMPLICATIONS

There are a number of important factors that make the continued economic evaluation of ART essential during the coming decade. The most obvious perhaps is that as new techniques and treatment options enter the market they should do so based on both their clinical and cost-effectiveness. A number of new techniques, such as oocyte freezing, preimplantation genetic diagnosis, and preimplantation

genetic screening, are being used to extend reproductive potential, improve pregnancy rates, or avoid the birth of children with genetic disease. However, very few economic evaluations have been undertaken before such technologies enter the market, and the ones that have been economically evaluated have often produced conflicting findings (71–73). Also, these newer techniques are almost universally not covered by either public or third-party insurance plans, rendering their economic assessment paramount to demonstrating their relative comparative effectiveness compared with existing technologies.

The economic assessment of different approaches to ovarian stimulation also warrants investigation as there is limited literature in this area (74). A noninferiority effectiveness trial of mild ovarian stimulation with single ET versus standard stimulation with two embryos transferred reported similar cumulative live birth rates during a 1-year period and lower costs per live birth; primarily due to lower indirect costs associated with caring for multiple birth infants and cases of OHSS that occurred in the standard ART group (75).

Without doubt, ART is increasingly being used to treat people who do not have infertility in the classic sense. Currently, women who are past reproductive age, are in non-traditional families, and those desiring gender selection for family balancing use ART procedures. It is reasonable to expect demand for such services will continue to grow. The increased pregnancy rates resulting from improved cryopreservation of eggs and embryos through vitrification has already resulted in demand by younger women to freeze eggs prophylactically to avoid the problem of reproductive aging. Society's obligations to provide economic support for such citizens will undoubtedly be a matter of debate and affected by the many unique characteristics of different cultures and countries. In the future, newer technologies enabling selection of higher potential embryos through genetic testing, optical methods, proteomics, metabolomics, or other biomarkers, will increase the probability of pregnancy through ART, and likely encourage more use of ART for elective reproduction. In addition, the use of stem cells and other developing cellular technology that enables early treatment of known disease or mitigation of disease predisposition will likely dramatically expand the market for ART and create novel medical, societal, ethical, and economic challenges.

With ARTs being increasingly accepted by patients and society as main stream medical treatments, it is important to ensure that funding is directed to those patients who will gain the most benefit from them, and that society is educated about the role that ARTs play in maximizing reproductive desires. For example, ART treatment is not cost-effective or necessary in couples who are likely to conceive naturally in a reasonable period of time (76), nor is autologous treatment cost-effective in older women (7, 77). Needless to say, overutilization of ART treatment serves neither patients nor society.

Finally, ARTs are primarily a treatment used in advanced economies such as North America, the Euro Zone, Japan, and Australia/New Zealand. However, with emerging market economies, such as China and India, having grown and strengthened impressively during the past decade, it is likely that ART demand will follow. The reasons for the likely

growth in ART markets in these countries are at least four-fold. As disposable incomes increase consumers have a greater ability to pay for expensive ART treatment; consumption patterns change as countries become more developed with more spending directed to personal services, technology, and medical care; as women become more educated they tend to have their first child later increasing the risk of age-related infertility (78); and the potential market in these countries is large due to the sheer size of the populations. For example, the number of households in China with a disposable income that classifies them as “middle class” by international standards is estimated to be almost double that of the United States by 2020 (78). Against this potential growth of ARTs worldwide, it is important that the lessons learned from developed countries are used to inform ART funding policies in emerging markets.

FINAL REMARKS

Infertility affects more than 80 million couples globally, representing significant personal suffering and burden of disease worldwide (79). The desire to have children is universal and people will go to great lengths and expense to realize this goal. However, what is an acceptable cost for ART treatment cannot be easily solicited from either a patient or societal perspective. Like any good or service, economic theory tells us that the cost willing to be paid is equivalent to the perceived benefit gained, but traditional tools used in health economic evaluations do not lend themselves to valuing a medical intervention that performs such a fundamental human function as reproduction. The oft-changing funding arrangements for ART treatments are testament to this. However, the empirical evidence that does exist indicates that ARTs are indeed good value money from a societal and patient perspective. With the changing nature of family structures, the trend to later childbearing, and the emergence of new techniques, demand for ART is likely to continue increasing worldwide. In the current climate of extreme pressures on health care budgets, it is important that the value of ART is made explicit to policy makers to ensure the equitable and cost-effective allocation of scarce health care resources.

Lastly, there is a body of evidence showing that economic incentives not only affect who can afford to access ART treatment but how ART is practiced, with significant implications for the health of ART children. This evidence must be used to inform funding arrangements for ART going forward. All children deserve the best possible start to life, including children born with the assistance of ART who are particularly vulnerable to policy decisions and market forces that play out before they are even conceived.

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