Cost-effectiveness of IVF compared to other infertility treatments; A United States perspective

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The relative cost-effectiveness of infertility treatments is an important issue. Couples desire infertility treatments that are not only efficacious- allowing for a short time to pregnancy, but also affordable, since infertility care is often not covered by insurance policies in the United States. Although the costs of treatment are often an individual's expense, insurance companies and society in general are frequently burdened the high costs of caring for premature infants that can result from multiple gestations induced by infertility treatments. Therefore, cost-effectiveness studies are important not only to the individual, but also to the health care industry and society in general.

In some instances, there is little debate about the preferred treatment for an infertile couple. For example, in cases of severe tubal disease, the low pregnancy rates after surgery makes IVF the clear treatment of choice from a cost-effectiveness standpoint (Van Voorhis *et al.*, 1997). Similarly, in a couple presenting with infertility and anovulation, oral ovulation induction medications are effective and inexpensive, making this the logical first line therapy. However, in some cases, the most cost-effective strategy to infertility care is not as clear. Couples with unexplained infertility or mild to moderate male factor infertility are the groups that have been most often studied in cost-effectiveness studies comparing IVF to intrauterine inseminations (IUI).

There are several important limitations when evaluating the relative cost-effectiveness of IVF and IUI. There have been relatively few randomized trials comparing these two treatments which limits the confidence we have in effectiveness comparisons, since most are based on retrospective cohort studies. On the cost side, many studies have reported infertility treatment charges as a surrogate for the actual cost of providing care. Charges can be artificial and don't necessarily reflect the true costs of providing a service. In addition, the outcome reported by many studies is the cost/delivery of at least one child. This outcome may not include the costs of caring for premature infants- a cost that can be substantial with the high rates of multiple gestations seen with infertility care. Finally, cost-effectiveness studies may be based on the outcomes and charges from a few centers limiting the more general applicability of the findings.

We have an extensive database that records the outcomes and costs of all infertility treatment cycles performed at our center, including both stimulated and unstimulated IUI cycles as well as IVF cycles. In a series of studies, we have previously compared the relative cost-effectiveness of common infertility treatments prescribed by reproductive endocrinologists for patients with all types of infertility. We found that IUI, whether done in a natural cycle, a clomiphene citrate-stimulated cycle or a gonadotropin-stimulated cycle, was significantly more cost-effective than one IVF cycle (Table 1). Although IUI cycles had lower delivery rates per cycle, ranging from 5–17% versus 28% per cycle for IVF at that time, the charges accumulated by IUI cycles were substantially less than those with IVF leading to a better cost-effectiveness ratio when expressed as a cost per delivery. In fact, the cost per delivery with IVF was three to fourfold higher than that with IUI (Van Voorhis *et al.*, 1997, 1998). We also found that

Table 1. — Relative cost-effectiveness of various infertility treatments at one academic medical center (Van Voorhis *et al.*, 1997)

Procedure	No. of couples	No. of procedures	No. (%) of deliveries	Multiple birth rate (%)	Cost per delivery ($)
IUI	54	103	6 (5.8)	0	8,674
CC-IUI	91	188	12 (6.3)	8.3	7,808
HMG-IUI	52	80	14 (17.5)	21.0	10,282
ART	136	155	43 (27.7)	30.0	37,028

all infertility treatments had a worsening cost-effectiveness ratio as women aged and, for women over the age of 40, the use of donor oocytes was significantly more cost-effective than doing IVF with a woman's own oocytes (Van Voorhis *et al.*, 1997, 1998). The use of cryopreserved embryos is a highly cost-effective treatment option for those couples who have excess embryos cryopreserved (Van Voorhis *et al.*, 1995). Finally, we reported that in couples where the male partner had extremely low sperm counts, as defined by the average total motile sperm count in the ejaculate from at least two samples of less than 10 million sperm, a lower pregnancy rate was achieved with IUI leading to worsened cost-effectiveness ratios (Van Voorhis *et al.*, 1997).

This finding led us to further study IUI cost-effectiveness using a retrospective cohort study from our center (Van Voorhis *et al.*, 2001). Our objective was to identify factors that affected pregnancy rates after IUI and IVF and then study the cost-effectiveness of these treatments based on these parameters. We were most interested in defining the effect of male factor infertility on cost-effectiveness of infertility treatments. We found that the best predictor of delivery following IUI was the average total motile sperm count (TMSC: calculated as seminal fluid volume X sperm concentration X motility percentage, from at least 2 samples) in the ejaculate. If the average TMSC was less than 10 million, we had very low delivery rates (less than 2%) with IUI. If the TMSC was between 10 and 30 million, IUI delivery rates were in excess of 5%/cycle but there was no additional value to hyperstimulation of the woman. If the TMSC was greater than 30 million, then good delivery rates were achieved with IUI and even higher pregnancy rates were seen with ovarian stimulation using either clomid or gonadotropins. Because IVF pregnancy rates were not affected by the TMSC, IVF was found to be more cost-effective than IUI for couples in which the male had a TMSC < 10 million. Above this threshold, IUI was more cost-effective than IVF. Thus, depending on the prognosis for an individual, the relative cost-effectiveness for various infertility treatments can differ (Van Voorhis BJ *et al.*, 2001). A number of other investigators have likewise found a cut-off value below which IUI is unlikely to be successful (reviewed in 5). Most studies have looked at the TMSC in the inseminant following processing for IUI rather than in the ejaculate as in our studies. These studies have identified TMSC cut-offs between .8 to 5 million (Van Weert *et al.*, 2004). When utilizing these values, there is poor sensitivity for predicting who will conceive but a high specificity predicting failure to conceive with IUI. However, the exact cut off likely needs to be based on the individual lab and sperm prep technique used.

There have been several prospective randomized trials comparing stimulated IUI treatments with IVF and both have concluded that IUI in general is more cost-effective than IVF (Goverde *et al.*, 2000, Karande *et al.*, 1999). However, findings from cost-effectiveness analyses are best used to decide allocation of resources for large populations of people. For the individual, clinical conditions and circumstances can influence the best course of treatment, even from a cost-effectiveness standpoint.

Time to conception is of importance to many couples both to alleviate the suffering and disappointment that comes from being infertile and to avoid the negative effects of aging on their reproductive potential. This factor was recently addressed in a prospective randomized trial termed the Fast Track and Standard Treatment trial (FASTT) trial (Reindollar *et al.*, 2009). This study enrolled women between the ages of 21 and 39 who had unexplained infertility and a normal ovarian reserve. In addition, severe male factor infertility was excluded as sperm concentrations of greater than 15 million motile sperm in the ejaculate were required for entry. The outcomes of the trial were both timed to pregnancy as well as cost-effectiveness of treatment. For this study cost-effectiveness was calculated by summing all insurance charges divided by the number of couples delivering at least one child. Charges were calculated from the time of randomization through hospital discharge of both the mother and baby or until one year after the protocol if pregnancy was not achieved. In the study, 243 women were randomized to a "conventional" treatment protocol which consisted of clomiphene citrate at 100 mg for 5 days

plus IUI for three cycles followed by FSH (150 IU/day) stimulated cycles plus IUI for three cycles followed by up to six IVF cycles. 256 couples were randomized to a "fast track" arm of the study consisting of clomiphene citrate at 100 mg for 5 days plus IUI for three cycles followed immediately by up to six IVF cycles. The "fast track" arm of the study had a significantly shorter time to pregnancy (a median time to pregnancy difference of 3 months) than the "conventional" treatment algorithm. The number of couples ultimately conceiving a pregnancy was the same in both arms but the charges per delivery were lower in the accelerated arm of the study. The authors concluded that, after use of clomid and IUI for couples with unexplained infertility, going directly to IVF was more cost-effective than using FSH-IUI cycles before IVF (Reindollar *et al.*, 2009). Couples in the accelerated arm were pregnant faster with fewer treatment cycles and with less cost. Importantly, there were equivalent rates of multiple gestations in the two arms of this study.

One limitation of most cost-effectiveness studies in infertility is the omission of the high costs of multiple gestations (Callahan *et al.*, 1994). Many analyses end with delivery and do not account for the high cost of neonatal care for prematurely born infants, often secondary to multiple gestations. This is a critical issue because it has been recently estimated that in the United States alone, the cost of preterm infants born after IVF therapy is nearly $1 billion/year. It is difficult to know where to draw the line for health care costs of infants born from infertility treatments. In the short term, these infants are very expensive to society but, in the long-term, they will often serve as productive, contributing members of society. Nevertheless, the multiple gestation issue is important and should be addressed in cost-effectiveness studies.

As we look to the future, it is clear that there may be shifting paradigms as to the most cost-effective treatment strategy for infertile couples. In recent years, there has been a marked increase in pregnancy rates with IVF, in general. Similar increases have not been achieved with IUI treatments. Indeed several recent studies modeling outcomes and costs have concluded that moving directly to IVF is more cost-effective than starting with IUI cycles for unexplained and mild male factor infertility (Bhatti *et al.*, 2008; Pashayan *et al.*, 2006). Particularly if the singleton delivery rate per cycle can be improved, perhaps with single embryo transfer, IVF may become the favored first line treatment for most causes of infertility. However, at this time, the balance of published studies still favor starting with a more conservative treatment regimen before moving to IVF for the treatment of unexplained infertility.

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