Modern ART:
Determining a Couple's Most Cost-Effective Embryo Transfer Decision

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April, 2007

Abstract[1]

The goal of this paper is to determine the optimal IVF embryo transfer decision for infertile couples, considering the costs and utilities associated with IVF, pregnancy, and raising a child through eighteen years. Using a Markov model, this paper predicts short- and long-term cost-effective ratios for three embryo transfer decisions by maternal age group. The results indicate that cost-effective decision making varies greatly by maternal age and whether parents operate under short- or long-term perspectives.

Introduction

In the United States, 6.1 million women between the ages of 15-44 are fertility-impaired, and 2.1 million married couples of child-bearing age are infertile (CDC, 2003). Clearly, the dream of having a child is not easily realized for all. Many of these infertile couples turn to assisted reproductive technology (ART) treatments in their attempts to build a family; however these treatments are often expensive and are rarely covered by health insurance. Despite the costs, ART procedures have become common enough that more than 48,000 infants were born from ART treatments in 2003, representing more than 1% of total US births that year (CDC, 2003). Even though these infants represented only about 1% of total births in 2003, they accounted for 18% of multiple births and more than 40% of triplets or higher order births nationwide (CDC, 2003). The increased risk for multiple births associated with ART treatments increases the likelihood of both poor

[1] Special thanks to Dr. Myers for his mentorship, devotion, attentiveness, and enthusiasm. Thanks also to Professor Alison Hagy and my classmates in Economics 198 and 199 for their insightful feedback and encouragement. Most of all, I would like to thank my family and friends for their support and love.
Upon graduation in May 2007, I will be moving to Baton Rouge, LA, where I will teach high school math as a Teach For America corps member. Please feel free to contact me with questions or comments at Theresa.Poulos@gmail.com.

infant and poor maternal outcomes. To illustrate, the CDC reported that 94% of triplet and higher-order ART infants were low birth weight, and 97% were born pre-term (CDC, 2003).

The reason for the high number of multiple births associated with ART treatment is the popularity of transferring multiple embryos during in-vitro fertilization (IVF), which is a common ART treatment. During the IVF procedure, eggs are combined with sperm in a lab to create embryos, which are then placed in a woman's body. Patients can elect to have either a single or multiple embryos transferred per IVF procedure. Since the procedure is very costly and rarely covered under insurance, patients often choose to transfer multiple embryos per procedure to ensure that at least one develops to term, despite the chance that all implanted embryos might progress to term.[2]

Unfortunately, the choice to transfer multiple embryos is inextricably linked to a higher likelihood of adverse pregnancy outcomes due to the increased risk that a patient will give birth to more than one infant (Martin and Park, 1999). Parents who choose to transfer multiple embryos are then more likely to have children that suffer from mental and physical handicaps, asthma, or cerebral palsy (ESHRE, 1999). These child health outcomes are associated with increased costs of childcare, as well as decreased quality of life for parents, who must invest additional time and energy in caring for their children. These parents also tend to suffer higher rates of anxiety, depression, sleep loss, and other disorders that impact upon their quality of life as a result of the demands of parenting a child with special health care needs (Thorpe et al., 1991). These costs and quality of life effects often follow parents through at least the first eighteen years of a child's life.

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[2] According to the 2002 ART Surveillance Report data, the majority of ART procedures involved transfer of more than one embryo: "Among women aged <35 years, 95% of procedures involved transfer of two or more embryos, and 53% involved transfer of three or more embryos" (Wright et al., 2005).

However parents may not fully consider these long-term impacts when they make their embryo transfer decisions. The tendency to transfer more than one embryo could reflect the fact that parents are heavily weighting the short-term costs, utilities, and gestational outcome probabilities associated with the IVF procedure itself, while excessively discounting the long-term costs and utilities associated with raising multiples and/or children with health impairments.[3] Couples who are in the midst of an infertility crisis might shift their short- and long-term valuations when presented with a medical opportunity to reverse their fate: knowing how it feels to be limited in options for starting a family, couples may want to take (what they see as) full advantage of any treatment opportunity by overvaluing short-term success of the treatment and discounting any long-term risks associated with the specifics of their treatment choice.

Given the short- and long-term economic implications of IVF treatment options, it is important to truly understand the optimal IVF embryo transfer decision. It is most important to consider the cost-effectiveness of different transfer decisions from the parental perspective, since parents are ultimately the ones making the transfer decision. Many early studies in the health economic infertility literature are empirical analyses that compare the cost-effectiveness of different treatment options, but these analyses only describe real data and therefore cannot predict the costs and benefits under alternative decision schemes. To sidestep these constraints, some of the more cutting-edge research has used mathematical simulations to create decision-analytic Markov models, which are able to analyze costs and outcomes of various infertility treatment decisions. However,

[3] Economic literature has long pointed to discounted utility when inter-temporal choices are considered: Paul Samuelson was one of the first to describe the discounted-utility (DU) model in 1937, and many other researchers have found patterns of inter-temporal discounting in empirical research, specifically in personal savings patterns (for a full review of time discounting literature, please refer to Frederick et al. (2002)).

most models have only considered the full costs of pregnancy complications, analyzing the costs of various embryo transfer decisions from an insurer's perspective.

Little et al. (2006) were the first researchers to break total costs down into those accrued by society, insurers, and parents. Their model compares the costs of transferring one through five embryos through IVF. They include estimates for the full costs associated with pregnancy in only their insurer and societal analyses. They simulate the parental perspective by assuming pregnancy costs to be covered by health insurance. They are also the first to consider an adverse clinical outcome of multiple births by including cerebral palsy as a final transition in their model. However their long-term cerebral palsy cost estimate is a lifetime cost estimate, and does not exclude health care costs that would be covered under insurance.

A more complete model would consider the long-term costs associated with complications beyond just cerebral palsy, but would consider only the costs that are truly incurred by parents by eliminating child health care costs that are commonly covered by insurance. Furthermore, long-term costs should be limited to a time period of eighteen years, at which point a child might begin covering his/her own costs of living. Additionally, no study to date has attempted to look at IVF and its outcomes in a health-related quality of life (HRQL) framework, using quality-adjusted life years (QALYs) to capture the total economic impact of infertility treatment options. Approaching the issue from a parental perspective necessitates consideration of quality of life, whereas the more typical insurer-based approach only required a cost analysis.

Therefore, I created a Markov model based on Little et al.'s work, but which expands upon their scope of adverse child outcomes to include long-term child complications beyond just cerebral palsy. I also limited the cost estimates for these long-term outcomes to exclude insurance-covered health care costs and extended them only through eighteen years of age. Furthermore, I incorporated utility estimates to generate a cost-utility analysis, using QALYs to obtain a more meaningful estimate for a couple's most cost-effective embryo transfer decision. I used my model to generate cost-effectiveness estimates for implanting one through three embryos per IVF treatment. Since I am interested in determining whether parents operate under a short- or long-term horizon when making their embryo transfer decisions, I ran my model to generate both short- and long-term cost-effectiveness estimates for the different transfer decisions.

My model suggests that a patient's most cost-effective transfer decision varies based upon whether short- or long-term costs and utilities are considered; the most cost-effective transfer decision also varied by maternal age.[4] Operating under a short-term perspective, couples <35 years would find it most cost-effective to transfer two or one embryo, depending on their cost-effective threshold. Couples 35-37 years old would most likely transfer three embryos, and parents 38 years and older would always transfer three embryos in the short term.

Operating under a long-term perspective, parents <37 years would usually find it most cost-effective to transfer a maximum of one embryo. If these younger parents place a high value on multiples over a singleton, they might transfer two embryos in the long-term. Parents age 38 and older would likely transfer two or three embryos in the long-term, depending on their cost-effectiveness threshold.

[4] Cost-effectiveness is measured in terms of the incremental cost-effectiveness ratios (ICERs) generated by my model. When I report an embryo transfer decision as the "most" cost-effective, it was dominant over the other two transfer decisions (both less expensive and more effective). If no transfer decision was dominant, the decision is reported as cost-effective depending upon a couple's threshold cost-effectiveness value---meaning the cost-per-QALY gained that they would pay for the IVF intervention.

My results indicate that as maternal age increases, it becomes more cost-effective to transfer more embryos in the both the short- and long-term. My results also demonstrate that parents who consider only short-term costs and outcomes would transfer more embryos as compared to parents who take into account all of the long-term costs and quality of life considerations associated with a transfer decision and its outcomes.

All of these estimates assume that parents are fully informed of the probabilities of gestational outcomes according to maternal age, and that they are aware of the long-term costs associated with these outcomes. Since real-world embryo transfer decisions match the short-term rates more closely than the long-term rates predicted by my model, my research suggests the importance of requiring providers to equip parents with all information pertinent to making informed embryo transfer decisions. This information would include the marginal probabilities of multiple pregnancy and pregnancy complications as the number of embryos transferred increases, in addition to literature on the long-term costs, burdens, and benefits associated with parenting multiples.

Section II of this paper reviews the most current literature on cost-effective analyses of infertility treatment options. Section III provides theoretical background on decision-analytic Markov models and their particular application to the analysis of different healthcare treatments. Section IV describes the details of the model used in this analysis. Section V details the data and sources used in the analysis. Section VI provides the cost-effectiveness results for the various IVF treatment strategies. Section VII analyzes the results and concludes with broader implications of this study.

Literature Review

Before decision-analytic mathematical models were developed to study the cost-effectiveness of infertility treatment options, descriptive empirical studies were the primary approach to synthesizing data on various procedures. Since then, mathematical simulations have used decision-analytic Markov models to compare costs of transferring single versus multiple embryos per IVF cycle. Each analysis has shown that from a insurer's perspective, it is least costly to transfer a single embryo per cycle as compared to two or more embryos, given the high costs and adverse outcomes associated with multiple births. However, none of these models fully account for the wide scope of adverse child outcomes or the long-term costs of childcare associated with the birth of multiples. Nor do they consider quality of life implications in their analyses. These are all very important factors to consider in calculating the total costs of infertility treatment, but no study to date has accounted for these additional measures.

An early empirical study comparing the cost-effectiveness of various infertility treatments included intrauterine insemination (IUI), IVF, and surgical procedures in its analysis (Van Voorhis et al., 1997). In analyzing pregnancy outcomes and treatment costs, these researches determined that IUI with hormone treatment was the most cost-effective infertility treatment in terms of cost per delivery. However, because this study did not differentiate between the numbers of embryos implanted per IVF cycle, it provides no comparison between the cost-effectiveness of single-embryo IVF transfers and IUI treatment. This subtle data distinction might have elicited different results, since multiple birth IVFs are the drivers of average total cost of IVF treatment. Van Voorhis et al. also noted that IUI was only an option for women with blocked fallopian tubes if they underwent expensive and risky surgery in addition to IUI. IVF could have been used successfully in these women, at a lower cost than for the surgery plus IUI. However, because this was a retrospective study, outcomes and savings between the IUI plus surgery option and the IVF option could only be hypothesized.

To more closely examine the differences observed by Van Voorhis, Pshayan et al. (2003) took a mathematical modeling approach to compare the outcomes and costs of IUI and IVF treatments. They created a decision-analytic Markov model to estimate the clinical and cost effectiveness of a primary offer of a full IVF cycle as compared to first providing an IUI, followed by an IVF for IUI failures. Their model predicted that initially offering IVF was the more cost-effective approach, despite the fact that IUI is a far less costly procedure than IVF. However these researchers only considered the cost of the procedure itself, and not the costs associated with pregnancy and birth.

Still, the suggested cost-effectiveness of IVF demonstrated by these early studies compelled researchers to focus more specifically on the IVF procedure, comparing the costs and outcomes related to the transfer of single versus multiple embryos per IVF cycle. De Sutter et al. (2002) developed a Markov model to compare the costs and gestational outcomes of single embryo transfer (SET) to double embryo transfer (DET). Not surprisingly, they found that more ART cycles are required to obtain the same number of children born following SET compared with DET. But they also found that because SET eliminates multiple births and their associated neonatal and pregnancy-related costs, there was no difference in cost per child born between SET and DET. Since publication, DeSutter et al.'s modeled findings have been empirically verified in randomized controlled trials and observational studies (Lukassen et al., 2005; Kjellberg et al., 2006; Fiddelers et al., 2006; Fiddelers et al., 2007); all of this research has verified that DET is the more costly transfer decision as compared to SET in terms of total procedure and pregnancy costs.

In 2006, Little et al. unveiled a similar but more in-depth Markov analysis. They expanded upon De Sutter et al.'s work by comparing the costs of transferring one through five embryos. Unlike prior research, they approached the costs from three different perspectives: society's, the infertile couple's, and the insurer's. They found that SET was least expensive from the societal point of view, but was most expensive from the parental perspective. From the parents' point of view, it was most cost-effective to transfer two through five embryos, depending on the mother's age. Little et al.'s work also broke new ground as it was the first model to incorporate any of the long-term costs associated with the birth of multiples. They included long-term morbidity and mortality costs (estimated as lost potential earnings) for children who develop cerebral palsy as a result of being a multiple birth baby. However their long-term cost estimate is a lifetime cost estimate that includes costs of healthcare, and therefore does not truly capture the costs incurred by the parents of a child with cerebral palsy. Additionally, there are no estimates for any of the other long-term adverse health conditions commonly associated with multiple births

Furthermore, any attempt to estimate a cost-effective decision from a parental point of view should include a measure to capture the impact of the decision on parental quality of life. Little et al. have no QALY measurements in their model, nor has there ever been an attempt to quantify the impacts of IVF in a QALY framework. In the past five years, there has been much work done using utilities to capture QALYs in decision analysis. Goldie et al. (2004) estimated the cost effectiveness of an HPV vaccine using cost per QALY ratios to determine optimal vaccination plus screening combinations. Mahadevia et al. (2003) incorporated quality of life measures in their decision model to estimate the cost-effectiveness of lung cancer screening with helical computed tomography in various efficacy scenarios. These are only two of many decision analytic models that have been recently developed to generate cost-effectiveness estimates in terms of QALYs. However utilities have not been used to analyze the cost-effectiveness of IVF or other infertility treatments in the same way.

The only literature that attempts to capture such a well-rounded parental valuation of IVF evaluates the procedure in a cost-benefit framework, with benefits measured as parental willingness to pay (WTP). A Swedish study by Granberg et al. (1995) and a US study by Neumann and Johannesson (1994) both found that couples place a high economic priority on infertility treatment; most infertile couples were willing to pay more than the direct cost of IVF treatment for the chance of having a baby. Clearly, infertility and the ability to conceive have a very real impact upon parental perceptions of quality of life, given their high WTP thresholds for IVF treatment.

Therefore, it is important to consider not just the costs of conception itself, but the more robust implications of gestation, birth, and quality of life associated with IVF treatment decisions and the birth of multiples. My model includes estimates for these additional costs and utilities, to best predict parental perceptions of the overall cost-effectiveness of different IVF embryo transfer decisions in both the short and long term.[5] In doing so, my model provides a more accurate cost-effective analysis than any in the

[5] As footnoted in the Introduction, I chose to look at differences between the short and long term cost-effectiveness given that Economic literature has long pointed to discounted utility when intertemporal choices are considered (for a full review of time discounting literature, please refer to Frederick et al. (2002)).

current literature. With this information, I determined which IVF treatment approach is most cost-effective from the parental point of view in terms of QALYs, and took note of differences in the most cost-effective decision based upon whether a couple placed more weight on short or long term costs and utilities.

Theoretical Framework

Mathematical models provide a useful framework for studying the costs and outcomes of different healthcare decisions. A particular type of model that is frequently used in clinical, epidemiologic, and economic evaluations is the Markov model. [6] Based upon a simple decision tree, Markov models are capable of modeling progression of disease in clinical situations where there is ongoing risk. They can also simultaneously handle both the costs and outcomes of different healthcare interventions, making them particularly useful in health economic evaluations. Given these capabilities, I will use a Markov model to compare the outcomes of three different IVF embryo transfer options.

A Markov model works by simulating the progression of a cohort through a finite number of different disease states (called Markov states), each of which is assigned a cost or utility. The time horizon of the analysis is split into equal time increments, called Markov cycles. During these cycles, patients transition from one state to another according to transition probabilities (p_1 through p_4 in Figure 1), which are the net probabilities of making a transition from one state to another during a single cycle. Transition probabilities are usually based on clinical or population data. Markov states that represent a short-term effect---by only transitioning to another state, and not back to

[6] Here I will provide a brief introduction to the theory and practice of Markov modeling. For a more comprehensive discussion, please see: Sonnenberg and Beck (1993), Briggs and Sculpher (1998), and Beck and Pauker (1983).

themselves---are called temporary states (ex: “Progressive Disease,” in Figure 1). A series of temporary states is called a tunnel state, since each state can only be visited in a fixed sequence. All Markov models must terminate in at least one absorbing state, which is a state that the patient cannot leave (exs: “Asymptomatic Disease” and “Dead,” in Figure 1).

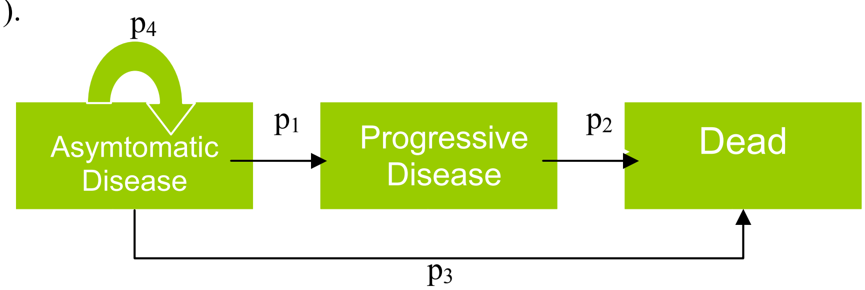


Figure 1: This shows a simple Markov-state diagram. Each box represents a Markov state, and each arrow indicates a possible transition. The “Dead” and “Asymptomatic Disease” boxes are absorbing states, the “p” variables are the transition probabilities, and “Progressive Disease” box is a transition state.

When the model is evaluated, the duration of time spent in each state is multiplied by the utility and/or cost associated with spending one cycle in that state, in order to generate expected costs and expected utilities:

$$\text{Expected Cost} = \sum_{s=1}^{n} t_s \times c_s \qquad \text{Expected Utility} = \sum_{s=1}^{n} t_s \times u_s$$

where t_s is the time spent in state s, c_s is the cost associated with spending a single cycle in state s, and u_s is the utility associated with spending a single cycle in state s. In a cost-effective analysis, the model is evaluated separately for cost and utility, and those numbers are then used to calculate cost-effectiveness ratios.

The Markov process is useful in decision analysis because it models the prognosis for a given patient; because it incorporates all events of interest, the decision analysis can be used to compare the values of two or more Markov processes.[7] In 1984, Hollenberg developed a method for this type of representation called a cycle-tree, in which the root of a tree is a decision node, with branches that are each Markov processes. These branches are called Markov cycle-trees. This method of representation is particularly useful when comparing different treatment options (See Figure 2). Such a model begins by assigning patients to one of the various treatment options under study. After this initial assignment, a Markov process begins on each treatment branch by simulating the progression of disease, given the transition parameters associated with that particular treatment. This modeling approach maintains appropriate symmetry in comparing the treatment options, allows for a great deal of flexibility when adjusting the model, and permits sensitivity analyses to be performed on any one of the Markov components.

[7] For a complete discussion of the use of the Markov process in decision analysis, please see Sonnenberg and Beck (1993).

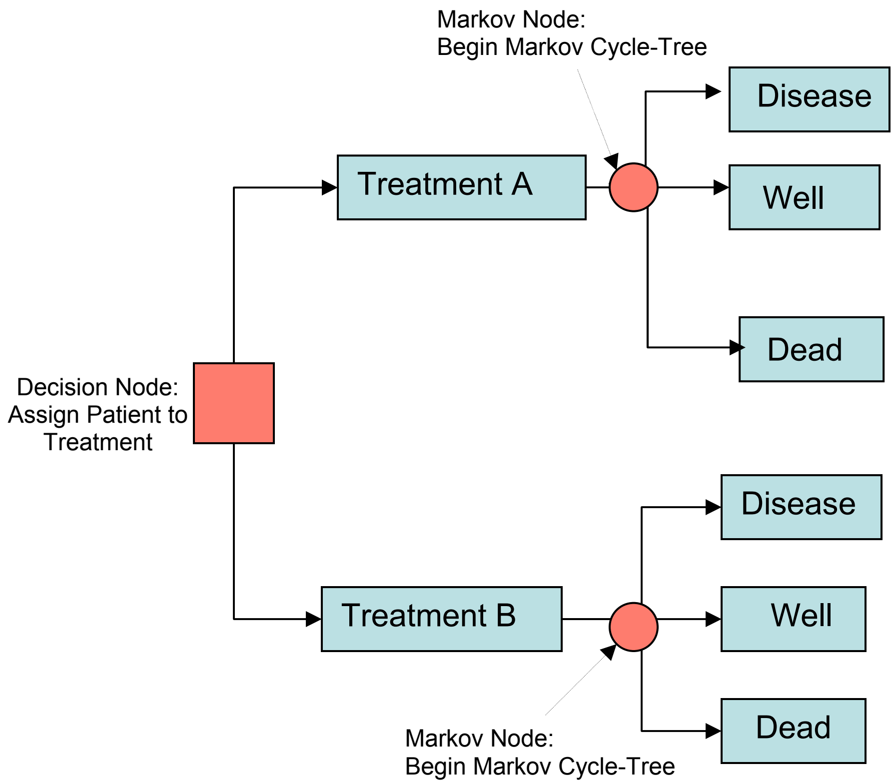


Figure 2: The square node in this Markov decision model is a decision node. The two circular nodes are Markov cycle-trees. The costs and utilities derived from the Markov cycle-trees can be compared, in order to determine the most effective or cost-effective treatment option.

I will utilize a Markov cycle-tree (similar to that shown in Figure 2) as I compare the cost-effectiveness of three different IVF embryo-transfer options. The Markov cycle trees will generate cost-effective estimates for the three embryo-transfer options, each of which will branch from the initial decision node. I can then compare the results from each of the three Markov cycle-trees in order to reach a final conclusion as to which embryo transfer decision is most cost-effective.

It is important to note that Markov modeling is not without inherent limitations. Modeling cannot perfectly represent clinical practice, where there are innumerable intangible variables for which to account. This is because the Markov model assumes path-independence; transition probabilities vary only by state, and cannot account for how or when an individual arrived in that particular state. This might become especially important as women undergo multiple cycles of IVF treatment. A woman who undergoes four unsuccessful cycles, or who undergoes two cycles that result in miscarriage before a successful third cycle, might have clinically different transition probabilities than a typical member of a cohort. But because the transition probabilities are constant between states, there is no way to account for changes in transition probabilities that might result as women undergo multiple cycles of IVF. Essentially, all members of the cohort are treated the same once they arrive in a state, because the transition probabilities are path-independent. This is more a limitation of Markovian Theory than of my specific model, and because this type of decision analysis is widely accepted in the literature (as previously discussed) it seems appropriate to use in generating my cost-effective analysis.[8]

Model Specifications

The Markov model used in this analysis was generated using the TreeAge Pro Software Suite. A visualization of the model, with the initial decision node and a single and simplified expanded Markov cycle tree, is provided in Figure 3. The initial decision node offers three "treatment" subtree paths: single-, double-, and triple-embryo transfer (SET, DET, and TET, represented in the $\mathbf{T_0}$ sector in Figure 3). Each of these three treatment nodes initiate identical Markov cycle trees, but with different transition probabilities according to the number of embryos transferred.

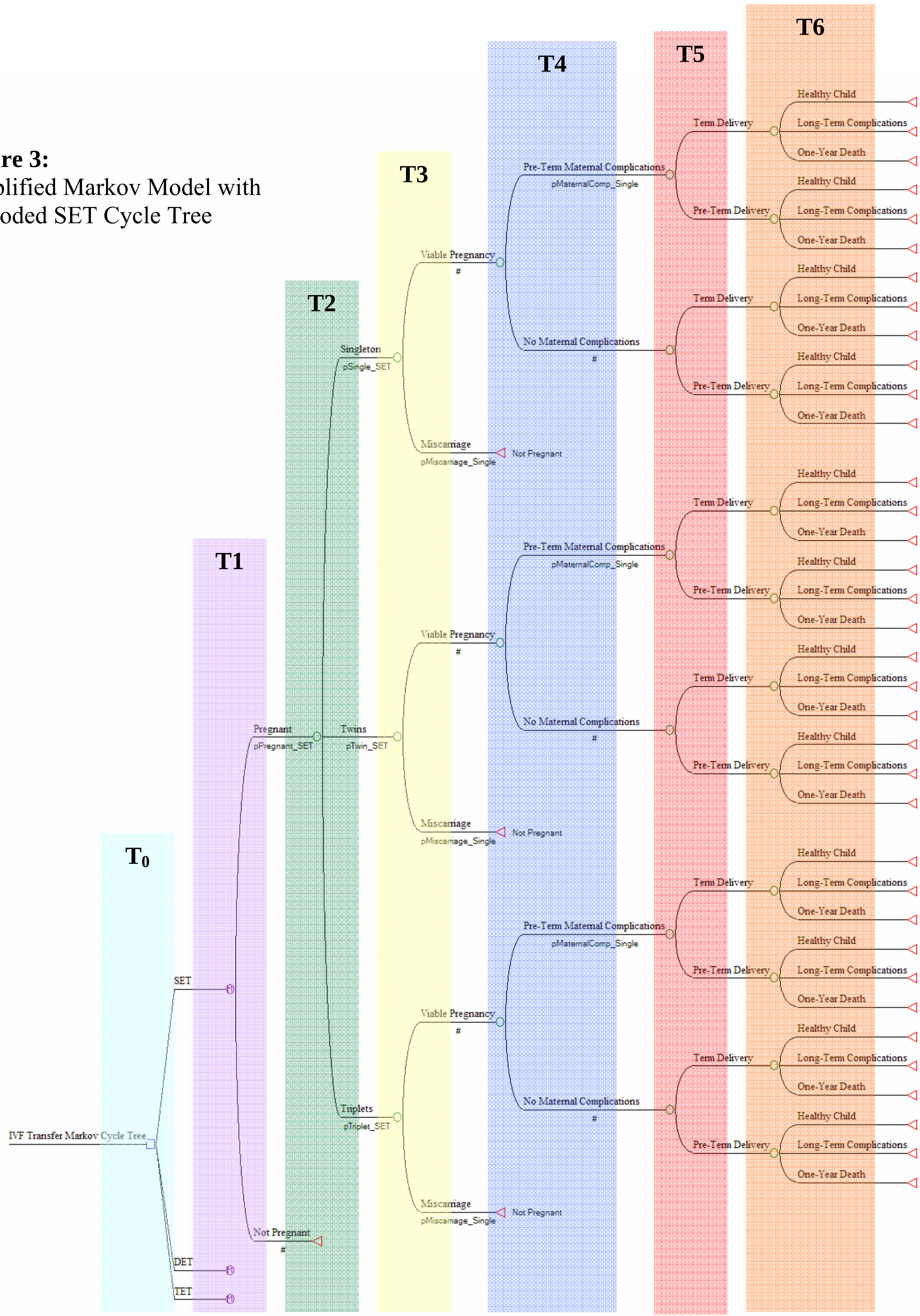
[8] For a more in-depth discussion of the limitations of the Markov modeling technique, please refer to Roberts (1992).

In Figure 3, the SET subtree is expanded to show the Markov transition states. The first transition (**T1** in Figure 1) is from treatment to either "pregnant" or "not pregnant." Using TreeAge's "_stage" feature, I modeled each woman as progressing through up to five IVF cycles; after five cycles, the woman will have either transitioned to the "pregnant" branch, or fallen into the "not pregnant" node, which is an absorbing state. Complicating this rather straightforward 5-cycle IVF transition procedure is the fact that older women are more likely to transfer fresh embryos, while younger women are more often able to freeze their embryos and have them available for frozen transfer.[9] I captured this age-adjusted difference in transfer decision---again using the "_stage" feature in the TreeAge programming---so that women in the younger age groups underwent more stages of frozen embryo transfer and women in the older age groups underwent more stages of fresh embryo transfer. Little et al. took a more complex approach in capturing the very specific percentages of women who would be able to transfer frozen embryos.[10] My model is not as complex as theirs, but I did refer to the same fresh versus frozen embryo transfer data as Little et al. to generate results that attempt to account for these different procedures.

[9] Fresh embryos are those created from eggs of the most recent menstrual cycle, while frozen eggs are generated in a preceding cycle, cryopreserved, and thawed just prior to transfer .Older women are more likely to undergo fresh embryo transfer because it is associated with higher rates of success. Furthermore, younger women more often have well-preserved fresh embryos available to transfer; older women's frozen embryos might have been frozen for too long to be safe and effective to use, or older women might have already used their frozen embryos in earlier procedures.

[10] Please see Table A1 in the Appendix for these percentages.

Figure 3:
Simplified Markov Model with Exploded SET Cycle Tree



The patients who reached the “pregnant” node then move to either the “singleton,” “twin,” or “triplet” transition state during the next transition (**T2** in Figure 3), again according to transition probabilities. From any of these nodes, the patient can then miscarry or have a viable pregnancy (**T3** in Figure 3). If a patient falls into the “miscarry” node and is not yet in the fifth cycle of IVF, she cycles back into the model at the point where she continues through another cycle of IVF, and the model resumes as previously described; if it is her fifth cycle of IVF, she terminates in the “not pregnant” absorbing state. A viable pregnancy can move to either “maternal complications” or “no maternal complications” (**T4** in Figure 3), and then from either of those states to “term delivery” or “pre-term delivery” (**T5** in Figure 3). Following those two cycles, the pregnancy itself is completely modeled, but there are still parental costs and utilities associated with child outcomes. Thus, the last transition considers possible child outcomes: the child/children can either be born healthy, be born with long-term complications, or die within two weeks of birth (**T6** in Figure 3).

Each of the Markov states is assigned a cost, a utility, or both a cost and utility, depending on the nature of the state. All states associated with a clinical procedure have costs corresponding with the medical costs of care. Some states include QALY measurements to capture utilities involved with particular clinical outcomes. The specific cost and QALY information is detailed in the data section that follows.

The model runs for a time horizon of twenty-three years: This allows two months for the IVF decision to be made and for the procedure to take place, and ten months for the duration and outcome of the pregnancy (a total of one year). This can happen up to five times, as each woman can undergo another IVF cycle---up to five IVF cycles---if the previous cycle was unsuccessful. After five years have passed, the model does not allow women to repeat the IVF and pregnancy cycle, but rather holds each woman in an absorbing state, which could be “not pregnant” or any of the various gestational outcomes. For the remaining eighteen years modeled in these absorbing states, the woman accrues costs and utilities corresponding to those states.

Data

The data used in the Markov model can be divided into three categories: transition probabilities, costs, and utilities. I gathered these data through an extensive review of clinical and population-based literature.

Transition Probabilities

In 1992, the Fertility Success Rate and Certification Act required all fertility clinics in the US to report their success rate data to the Centers for Disease Control and Prevention (CDC). The CDC then publishes this data in a report entitled: “Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports.” This report summarizes data from 399 fertility clinics nationwide, and provides the most recent and comprehensive data on the type, number, and outcome of ART cycles performed in US clinics. Of particular use in my study are the live birth rates per number of embryos transferred and the maternal miscarriage rates, both of which are reported and published by maternal age group. A 2002 Surveillance Supplement and 2003 Full Report provide the most recent data available, which I used in the first three transition probabilities in my model (this data is shown in Table 1, these probabilities correspond to the transitions in **T1**, **T2** and **T3** in Figure 3).

Pregnancy rates (**T1** in Figure 3) were derived from the live birth rates and the miscarriage rates.[11] In the 2003 report, data on miscarriage rates were reported for each maternal year of age, not by age subgroup. Therefore, I calculated an average rate to correspond to each maternal subgroup described in the IVF live birth rate data.[12] Data on the rate of singleton, twin, and triplet live births by number of embryos transferred were used as reported (Table 1, **T2** in Figure 3). In looking at the data, it becomes obvious that the likelihood of pregnancy is very different between maternal age groups. For example, given that a single embryo is implanted, a 35 year-old has a probability of 0.48 of getting pregnant, as compared to a probability of 0.05 for a woman between 41 and 42 years-old. Along the same lines, there is a higher rate of miscarriage among older women: 0.11 for women under 35, as compared to 0.38 for women aged 41-42 (**T3** in Figure 3). This raw data reinforces the need to run the model for all four different maternal age groups. Given the lower rates of pregnancy and successful birth among older women, the most cost-effective number of embryos to transfer would likely be higher in older women.

Table 1: IVF Success Rates (Probability Inputs for Markov Model)

	Maternal Age (years)			
	<35	35-37	38-40	41-42
Pregnancy (no. of embryos)				
1	0.48	0.38	0.15	0.05
2	0.52	0.44	0.17	0.10
3	0.52	0.46	0.22	0.12
Miscarriage	0.11	0.15	0.23	0.38
Singleton (no. of embryos)				
1	0.98	0.99	0.97	1.00
2	0.64	0.70	0.81	0.94
3	0.58	0.64	0.73	0.79
Twins (no. of embryos)				

[11] These rates were derived in much the same way that Little et al. (2006) derived pregnancy rates in their research.
[12] This method again mimics the approach taken by Little et al. in analyzing the ART Report data.

1	0.02	0.01	0.03	0
2	0.36	0.29	0.19	0.06
3	0.35	0.32	0.24	0.20
Triplets (no. of embryos)				
1	0	0	0	0
2	0	0.01	0	0
3	.07	0.04	0.03	0.01

Sources: CDC, *ART Success Rates, 2003;* Wright et al., *ART Surveillance---United States, 2002*

Progressing through the model, maternal complication transition probabilities (**T4** in Figure 3) were estimated using antenatal maternal hospitalization rates. The maternal complications most common in multiple birth pregnancies include pregnancy-induced hypertension, toxaemia, gestational diabetes, premature rupture of membranes, and caesarean section delivery (ESHRE, 2000).[13] When serious, these complications are treated during antenatal hospitalization. Unfortunately, the antenatal hospitalization rate does not capture cases where maternal complications are not severe enough to warrant hospitalization. However, antenatal hospitalization rate captures the most costly and clinically meaningful maternal complications, and therefore speaks to the most substantial costs and dis-utilities of multiple birth pregnancies. The rates used in this model are those reported in 2000 by the European Society of Human Reproduction and Embryology (ESHRE) (Table 2). This data is drawn from a large cohort study, and is regularly used and cited in both American and international research.[14] In looking at the data, it becomes clear that the rate of complication is much greater in higher-order births (12.2% among singleton mothers, compared to 56.9% among triplet mothers). This data would seem to favor a single-embryo transfer decision, so as to avoid the high risk of negative maternal health outcomes associated with the birth of multiples.

[13] See Table A3 in appendix for the rate of specific complications according to the number of fetuses.
[14] A host of peer-reviewed journal articles that cite the ESHRE group's studies can be found via a PubMed search, available at: http://humrep.oxfordjournals.org/cgi/content/abstract/16/4/790.

Risks for pregnancy complications also increase with age, so I incorporated adjusted odds ratios into my maternal complication transition probabilities. These ratios were taken from a recent study that used national vital statistics data to evaluate the risks of pregnancy complications and adverse outcomes by maternal age (Luke and Brown, 2007).[15]

The next transition probability in the model requires the rate of term versus pre-term delivery (**T5** in Figure 3). These probabilities are again taken from the ESHRE data, and are the same probabilities used by Little et al. (Table 2). The data show that high-order birth babies have a greater probability of being premature and low birth weight, as reflected in Table 2. As was the case with maternal complications, the differences in rates of child complications between singleton and higher-order births (a total of 92.0% of triplets are premature, compared to only 9.3% of singletons, and 94.6% of triplets are low birth weight, compared to only 10.7% of singletons) will likely impact parental embryo transfer decisions, given the likelihood of negative child health outcomes among multiple-birth pregnancies.

Additionally, some pre-term babies die within two weeks of birth, which is another transition included in the model (**T6** in Figure 3). Data for this transition come from Callahan et al.'s 1994 study of 13,206 women who used ART techniques to become pregnant. The researchers followed the cohort through pregnancy and recorded the outcomes and hospital charges associated with delivery and follow-up care. Data from this study will also be used in my model's cost estimates, which will be described more thoroughly in the following section.

[15] Please see Table A4 in the Appendix for these adjusted odds ratios.

Table 2: Pregnancy Complication Probabilities

	Singleton	Twins	Triplets	Source
Antenatal Maternal Hospitalization rate	12.2%	30.5%	56.9%	ESHRE Capri Workshop (2000)
Premature, 37-32 weeks	8.1%	37.8%	68.4%	ESHRE Capri Workshop
Premature, <32 Weeks	1.2%	5.1%	23.6%	ESHRE Capri Workshop
ELBW (<1500g)	1.6%	6.2%	27.0%	ESHRE Capri Workshop
LBW (2500-1500g)	9.1%	50.7%	67.6%	ESHRE Capri Workshop
Two-week Survival	97.4%	94%	86.3%	Callahan et al. (1994)
Cerebral Palsy	0.28%	1.26%	4.48%	Pharoah and Cooke (1996)
Limitation in more than one ADL	4.07%	16.17%	29.05%	McCormick et al. (1991)
Asthma	1.38%	7.2%	12.97%	McCormick et al. (1991)

The final transitions (**T6** in Figure 3) consider the rates of long-term complications that are relatively common among low birth weight (LBW) and extremely low birth weight (ELBW) babies. These include the probabilities that a child will be born with cerebral palsy, limitations in activities of daily living (ADLs), or asthma. Using data on the long-term prevalence of these complications in LBW and ELBW children and adolescents (McCormick et al., 1991), I derived the rate of each of these complications among singletons, twins, and triplets, given the rate of LBW and ELBW infants among singletons, twins and triplets[16]. In looking at these rates, presented in Table 2, it is clear that babies in higher-order births have a greater chance of long-term complications. These increased rates of long-term complications among multiples could affect the ideal parental embryo-transfer decision such that parents would transfer one embryo, to avoid the health risks associated with higher-order births.

[16] See Table A4 in the Appendix for the data used in these calculations.

Costs

Each transition state is assigned a monetary cost, which includes all costs related to that transition. To begin, the first state (**T_0** in Figure 3) requires a female patient to undergo a fresh embryo transfer IVF cycle. The estimated direct cost of a single IVF treatment cycle in 2006 is $12,400 (American Society for Reproductive Medicine). This is an average national cost, but can vary by provider and region. Additional costs include lost wages due to initial doctor appointments, the procedure itself, follow-up doctor appointments, and recovery time. Previous studies have estimated this time lost as one week per partner, which amounts to total lost wages of $1,364 per procedure. Thus, total cost per fresh embryo transfer procedure sums to $13,764 in direct and indirect costs[17] (Table 3).

As mentioned previously, some women choose to undergo frozen embryo transfer after having undergone a cycle of fresh embryo transfer. Women who undergo a frozen cycle must have retrieved and retained the frozen embryos from a previous fresh embryo transfer, so every woman in my model went through an initial fresh embryo transfer and incurred those costs. As reported in Table 3, the cost of frozen embryo transfer is estimated at an average of only $5,346 per procedure as compared to the full price of the fresh embryo transfer (Little et al.). This estimate includes costs for lost wages. The additional cost to have retrieved and frozen the eggs during the initial fresh transfer is estimated at $699 (Little et al.). I therefore estimated the first frozen embryo transfer cost at $6,045, and $5,346 for each frozen transfer thereafter. Because younger women more

[17] Table A2 in the Appendix includes all of the initial IVF treatment cycle costs.

often undergo frozen embryo transfer, the total IVF costs incurred by younger couples is likely to be much lower than the costs incurred by older couples. This cost difference would suggest that younger women might find it more cost-effective to transfer fewer embryos per IVF procedure than older women, because they are able to undergo the procedure more times, at a lower cost.

Table 3: Initial IVF Treatment Cycle Costs

	Cost	Source
IVF Cycle, Fresh, 2006	$12,400	American Society for Reproductive Medicine (2003)
Total Lost Wages per Couple (2006)	$1,364	Neumann et al. (1994); US Department of Labor, Bureau of Labor Statistics
Total Cost per IVF Procedure, Fresh	$13,764	
Total Cost for first Frozen IVF Procedure	$6,045	Little et al. (2006)
Cost for each additional Frozen IVF Procedure	$5,346	Little et al. (2006)

Moving through the model (to the **T3** state in Figure 3), the medical costs of miscarriage were calculated using cost and incidence data on the two most common types of miscarriage treatments: expectant care and surgery[18] (You and Chung, 2005; Butler et al., 2005). Total cost per miscarriage was estimated at $1330.65.

Proceeding to the next transition state (**T4** in Figure 3), I first referred to the costs associated with maternal complications are those estimated by Callahan et al (1994). These incorporate estimates for length of hospital stay,[19] incidence of caesarean section,[20] and delivery at less than 38 weeks[21] unique to singleton, twin, and triplet pregnancies. However, Callahan et al.'s cost data is from 1991, so I adjusted it to reflect 2006 dollars

[18] See Table A5 in Appendix for data and calculations.
[19] 4.0 days for the mother of a singleton neonate, as compared with 6.8 days for the mother of twins and 14.1 days for the mother of triplets
[20] 24%, 59%, and 86%, for singleton, twin, and higher-order multiple-gestation deliveries, respectively
[21] 24%, 67%, and 93%, for singleton, twin, and higher-order multiple-gestation deliveries, respectively

according to the Consumer Price Index (Table 4). While this data might seem dated, it is the most recent and complete available.

Callahan et al. made similar cost estimates for the total hospital charges for the birth of a singleton, twins, and triplets, which are used as estimates in the **T5** transition state in Figure 3. In generating these estimates, Callahan et al. considered the special costs associated with the rate of term and pre-term delivery, since pre-term babies are at much higher risk of being low or extremely low birth weight[22]. Thus, Callahan et al's cost estimates consider the average length, rate, and costs of neonatal hospital stays[23] and/or NICU stays,[24] given that singletons, twins, and triplets have different rates of pre-term delivery. Again, Callahan et al.'s estimates are in 1991 dollars, so I adjusted them to reflect 2006 dollars (Table 4).

Table 4: Costs of Complications and Pre-Term Delivery -- Maternal and Child Medical Care

	Singleton	Twins	Triplets	Source
Maternal Complication, Hospital Charges (2006 dollars*)	$7,161.09	$11,828.09	$22,763.63	Callahan et al. (1994)
Lost Maternal Wages due to Complications (days spent hospitalized x 8 hours per day x $17.05/hr)	$545.60	$927.52	$1,923.24	Callahan et al. (1994); US Department of Labor
Total Cost of Maternal Complications	$7,706.69	$12,755.61	$24,686.87	
Total Hospital Charges for Pre-Term Childcare (2006 dollars*)	$7,411.24	$44,340.16	$139,707.91	Callahan et al. (1994)

* Calculated using CPI inflation calculator (http://data.bls.gov/cgi-bin/cpicalc.pl)

With even just a quick glance at the data presented in Table 4, it becomes obvious that much of the costs for any of these pregnancy outcomes would be covered under health insurance. Because I am considering the costs from the parental perspective, and

[22] Low birth weight is defined as 1500-2500g; extremely low birth weight is defined as less than 1500g. Infants with a gestational weight below 2500g tend to have significantly longer neonatal hospital stays[16] and are at increased risk for neonatal-intensive care unit (NICU) stays[17].
[23] 4.6, 8.2, and 10.0 days, for singleton, twin, and higher-order births, respectively
[24] 15% of singletons, 48% of twins, 78% of triplets

because I am basing my work upon Little et al.'s earlier study, I will choose to assume the same insurance scenario modeled in their work. Little et al. assumed that parents had a health insurance plan that covered obstetric and neonatal care, offering a 20% coinsurance and a $2,000 deductible. Therefore, I will input $2,000 as a parental cost estimate per live birth.

For the long-term child complication transition states (i.e. asthma, cerebral palsy, and limitation in more than one ADL), I generated estimates for the extra costs of caring for children in each of the states, through age 18. By using 18-year estimates instead of lifetime cost estimates, my model is limited to cost considerations within parental purview. I also attempted to eliminate most of the direct healthcare costs that would be covered by health insurance since again, parents would only be paying the insurance co-pay and not the entire amount of the healthcare charges. I found cost estimates for the indirect costs of care for children with asthma and cerebral palsy in published literature (Table 5). To estimate the costs of raising a child who is limited in more than one ADL, I used data from a CDC report that broke down the lifetime economic costs (direct and indirect costs) of living with mental retardation, hearing loss, and vision impairment (Honeycutt et al., 2004). Using the cost breakdown in this report, in addition to special education costs reported in the US Department of Education's Special Education Expenditure Project (2003), I generated an estimate of $131,595 in extra costs for the parents of a child who is limited in more than one ADL, through age 18.[25]

These long-term costs only contribute to the already higher short-term costs associated with the birth of multiples, as described previously. Together, this cost data

[25] For a breakdown of this data, please see Table A6 in the Data Appendix.

suggests that the most cost-effective embryo transfer decision would be SET, to limit the costs of short- and long-term health complications associated with multiples.

Table 5: Indirect and Non-Medical Costs to Care for a Child through age 18

Condition	Cost (per child, through age 18)	Source
Asthma	$2,430	Weiss and Sullivan (2001); Ungar et al. (2001)
Cerebral Palsy	$153,000	Honeycutt et al. (2004); Davidoff (2004);
Limitation in More than One ADL	$131,595	Honeycutt et al. (2004); SEEP (2003); Davidoff (2004)
Healthy Child	$237,000	USDA report, written by Shultheis and Webster (2000)

Finally, I compare the costs of raising a single child versus twins or triplets. For parents who plan to only have one child, the costs of regular childcare for an additional child can be quite considerable. Since I consider parents who undergo the child-rearing process for the modeled attempt only (not parents who have other children, or who might attempt to have children again after the modeled period[26]), the cost per child above a singleton are important to include in my calculation. Therefore, I included an estimate for the non-medical costs of raising a child through age 18 by assigning every child a cost of $237,000[27] (USDA, 2000). This cost is an estimate that was calculated based upon the typical costs of raising a child that are accrued by an average, middle-class American family; because it is a variable of such great magnitude that is largely based on generalized, population-based assumptions, it will be an important value to further

[26] This is a limitation of my model, as some parents plan to have additional children in succession, and therefore will eventually accrue the long-term childcare costs of more than one child. My model's parameters do not allow me to consider these couples who parent more than one child in succession. If, however, this model were to be applied to parents of more than one child, it could be considered as the couple's final IVF attempt (after already having conceived other children), so that any children beyond a singleton birth would result in additional, unanticipated costs of childcare that the couple would not have desired or planned to incur.
[27] This estimate is inflation-adjusted.

examine in sensitivity analyses. While healthy children were assigned only this base cost, this cost was added to those reported above for children with long-term complications.

Furthermore, the literature suggests that there are few, but not many, economies of scale associated with raising multiples. For example, families with multiples cannot save by re-using cribs or hand-me-down clothing because all of the children need those things concurrently. However, instead of paying twice the amount for a babysitter---as would be suggested if I simply doubled or tripled the base costs of childcare for twins or triplets---parents of multiples might only marginally increase the amount they pay to a babysitter. Citing such examples, the literature suggests that it would be fair to estimate the cost of raising twins at 1.8 times the cost of raising a singleton, and the cost of raising triplets at 2.6 times the cost of raising a singleton (American Society for Reproductive Medicine). I used these adjustments factors in making my final cost estimates for raising twins and triplets.

Utilities

The literature on utilities is far less developed than that on clinical and population-based costs and disease prevalence. However, most researchers recognize that it is essential to somehow capture health-related quality of life (HRQL) in a complete cost-effective analysis. Especially in an area of study as sensitive as infertility, it is difficult---yet essential---to consider HRQL. Therefore, I have placed base-case utility estimates in my cost-effective model, which can be adjusted during sensitivity analyses to determine the magnitude of parental utility necessary to allow for different embryo-transfer decisions to be cost-effective.

These base-case estimates come from the Health and Activity Limitation Index (HALex), which was collaboratively developed by the National Center for Health Statistics (NCHS) and health status measurement experts. It was used in the analysis of data from the National Health Information Survey (NHIS) to determine HRQL scores for 30 different health conditions. These scores are on a scale from 0.1 (lowest health state) to 1.0 (optimal health). From this data set, I obtained HALex scores for Female Genital Cancer and Male Prostate Cancer, which I used to derive a utility estimate for IVF failure (Table 6). Although infertility is not a life-threatening condition such as cancer, it is a chronic condition that affects the reproductive system and severely limits one's life options---and by extension, the quality of their daily living. Furthermore, the two cancer scores are very close, at 0.68 for female genital cancer and 0.65 for male prostate cancer, suggesting that an estimate in that range might be acceptable. Therefore, I will make an estimate of 0.68 for the utility associated with IVF failure, a rough guess based upon the little literature that is available; because some sort of approximation is essential for my model, this utility value of 0.68 for IVF failure will serve as my base case estimate, which I will further explore by varying in sensitivity analyses. This assumption of 0.68 could significantly alter my cost-effective results because DET and TET result in much lower rates of IVF failure (see rates in Table 1); so it is very important to fully tease out the a wide range of utility values for this variable in sensitivity analyses.

For the parental utilities assigned to different child outcomes, I turned to work that has been done in the psychology field. Again, the information on these types of utilities is sparse, so my estimates rely heavily upon just a few sources. Saigal et al. (2000) used surveys to generate HALex estimates for HRQL utility estimates for the parents of physically limited ELBW children (Table 6). These same researchers also interviewed the children of these parents to determine the children's self-assessed HRQL utilities. They found a difference of 0.09 between the self-assessed and parental utility estimates, with the parents having a higher quality of life than their physically handicapped children (not unexpected).

However no research has been done to generate HRQL estimates for parents of children with asthma or cerebral palsy. Looking at the HALex dataset, I found that the self-assessed utility for living with asthma is 0.81, which is very close to the self-assessed score of 0.82 reported by the physically limited ELBW adolescents in the aforementioned study. Because these scores were similar, I used the 0.92 score reported by the parents of the physically limited ELBW adolescents to estimate 0.90 as the parental HRQL score for parents of asthmatic children. The self-assessed HRQL score for individuals living with cerebral palsy is very low, at 0.39. This score is lower than the estimate for IVF failure, and in my model, I consider any child birth optimal over IVF failure, because becoming a parent would be the ultimate goal of the IVF patient. Therefore, I estimated the HRQL score for the parent of a child with cerebral palsy to be 0.75, which is just above the maximum score I assign to IVF failure. This captures the disutility associated with such a poor health outcome, but also the utility associated with the ultimate goal of parenting.[28] Given the increased risk of cerebral palsy among multiples, incorporating this low HRQL measure to the model might cause a very real decline in the total cost-effectiveness of transferring more than one embryo. However, because the overall incidence of cerebral palsy is very low, even among multiples (0.28% among singletons, up to only 4.48%

[28] Again, this method of estimation relies heavily upon assumptions, and points to an incredible need for research in this area of psychology and utility literature.

among triplets; see Table 2), the overall impact of this low utility score may not be significant enough to affect the cost-effectiveness of embryo transfer decisions.

Table 6: Utility Scores

Outcome	HALex Score	Source
Female Genital Cancer	0.68	Gold et al. (1998)
Male Prostate Cancer	0.65	
IVF Treatment Failure (base case)	0.68	Estimated
Self-Assessed Utility Scores, by Adolescents Limited in more than 1 ADL	0.82	Saigal et al. (1994)
Utility Scores Reported by Parents of Adolescents Limited in more than 1 ADL	0.91	Saigal et al. (2000)
Cerebral Palsy	0.39	Gold et al. (1998)
Utility Scores for Parents of Children with Cerebral Palsy	0.75	Estimated
Asthma	0.81	Gold et al. (1998)
Utility Scores for Parents of Children with Asthma	0.90	Estimated

Sensitivity Analyses

While reliable probability and cost data does exist, one of the most interesting capabilities of the Markov decision analysis is that it will allow me to vary the cost and utility variables that were based on assumptions and estimates, to see whether the estimates for the data that does not exist significantly alter the model's cost-effectiveness outcomes. For example, there are no HRQL scores for the chronic fatigue, stress, and social isolation often described by parents of multiples (American Society for Reproductive Medicine). Nor are there any utility estimates to suggest that some parents may value multiples over singletons, especially among couples who cannot easily conceive. In order to consider these impacts upon parents' perceptions of the best embryo transfer decision, I ran sensitivity analyses in my model. To do this, I assumed a utility equal to one for all healthy children in my base case model; then I altered the utilities assigned to different gestational outcomes in subsequent runs of my model. In one trial, I held the utility for a singleton equal to one, but valued twins and triplets at 0.85 to model parents whose HRQL is lower due to the chronic fatigue and social isolation associated with parenting multiples. In another trial, I valued singletons at 0.85 and twins and triplets at one, to model parents who would greatly prefer any multiple gestation outcome over a single child.

Three other sensitivity analyses more fully explored the most sensitive cost and utility values in the long-term cost-effectiveness model. One looked at varying IVF failure utility values in all maternal age groups---ranging from values of 0.55 to 0.95---to see how those values altered a couples' cost-effective transfer decision. Another sensitivity analysis relaxed the utility assigned to healthy child outcomes to less than one. A final sensitivity analysis altered the costs of raising a healthy child to see how those costs affected the most cost-effective transfer decision.

Findings

The goal of this paper is to determine the optimal IVF embryo transfer decision for infertile couples. The optimal decision will be the one that is most cost-effective from the couple's perspective, with costs captured in dollars and effectiveness captured in QALYs. In order to generate cost-effectiveness estimates under different embryo transfer strategies, I constructed a decision analytic Markov model and modeled three different embryo transfer options: SET, DET, and TET. Expanding upon previous studies, my model considers the costs of raising the infant(s) through eighteen years after birth. This allows for consideration of the adverse outcomes, decreased utilities, and increased costs associated with the birth of multiples, which is more common under DET or TET.

Because my model also includes a proxy for the decreased utility associated with IVF failure, my analysis considers how the additional costs and decreased utilities associated with long-term child complications (more common when more than one embryo is transferred) interact with the IVF failure utility estimate (with failure being more common when only one embryo is transferred). Furthermore, by isolating the long- and short-term costs, I generated cost-effectiveness estimates for both long-term and short-term perspectives; these estimates may better explain how parents make real-world embryo transfer decisions, as their present duress might compel them to overvalue a short-term "fix" and discount the resulting long-term costs and consequences.

Outcome Results

Before discussing the cost-effectiveness estimates generated by my model, I will first verify its validity by comparing the IVF outcomes and costs to outcomes and costs reported in previous studies. The IVF outcomes generated by my model are similar to those of Little et al's. Table 7 shows the gestational outcomes and complications per 10,000 women under the different embryo transfer decisions, by maternal age group. Little et al. reported their outcomes in the same way in their study (births per 10,000 women), and their rates were consistent with those generated by my model. In all age groups and under all transfer decisions, the gestational outcomes generated by our models never exceed a 7% difference of each other, and are often within a range of 2% difference. These small variances are likely due to the more complex approach that Little et al. took to model fresh versus frozen embryo transfer.

The general trend in the outcome data is as expected: in every age group, the total number of live births, the total number of multiple births (either twin or triplet), and the total number of long-term child complications increases as the number of embryos transferred increases. These outcomes are intuitively logical, because as more embryos are transferred, there is a higher likelihood that at least one of them, if not more, will develop to pregnancy. Furthermore, as previously described in the Data Section of this paper, with multiple births come higher rates of long-term child complications.

Table 7: Outcomes for Five Cycles of In Vitro Fertilization per 10,000 Women per Age Group (with Little et al.'s Outcomes in Parentheses)

Embryo Transfer Decision	Live Births	Singleton Births	Twin Births	Triplet Births	Cerebral Palsy
Women Under 35 y					
1	9,132 (8,945)	8,979 (8,740)	153 (205)	0 (0)	28 (26)
2	9,187 (9,226)	6,378 (5,916)	2,809 (3,246)	0 (64)	61 (44)
3	9,216 (9,265)	5,807 (5,361)	2,832 (3,244)	577 (660)	88 (53)
Women 35-37y					
1	6,310 (6,815)	6,245 (6,720)	65 (95)	0 (0)	25 (19)
2	8,644 (8,665)	6,568 (6,076)	2000 (2,521)	76 (69)	55 (39)
3	8,715 (8,881)	6,171 (5,652)	2,237 (2,851)	307 (378)	69 (45)
Women 38-40 y					
1	4,428 (4,152)	4,326 (4,044)	102 (107)	0 (0)	13 (12)
2	7,009 (6,879)	5,974 (5,591)	1,035 (1,288)	0 (0)	33 (26)
3	7,835 (7,823)	6,160 (5,736)	1,471 (1,894)	204 (193)	52 (35)
Women 40-42 y					
1	2,166 (2,152)	2,166 (2,152)	0 (0)	0 (0)	6 (6)
2	4,107 (3,980)	3,937 (3,738)	170 (242)	0 (0)	14 (12)
3	4,955 (4,947)	4,224 (3,957)	689 (961)	42 (29)	26 (19)

Also apparent in Table 7 is the notable difference in IVF success between women in different age categories. Older women have a significantly lower chance of becoming pregnant at all (total live births in the under 35 cohort are more than two times the total live births in the 41 to 42-year old cohort), regardless of the embryo transfer decision. This explains why the overall rate of long-term child complications also decreases as maternal age increases, despite the fact that older mothers are inherently at higher risk for poor birth outcomes. This observation will be important to remember when looking at total long-term expected cost per woman under the different embryo transfer strategies.

Cost Results

The cost data generated by my model is available in Table 8. To place my results in context with previous literature, I adjusted my model to include only the long-term costs of cerebral palsy so that I could compare my cost results to those of Little et al.[29] As presented in Table 8, the parental costs generated from this base case model are similar to those generated by Little et al.'s model. Any differences can again be attributed to their more complex approach to modeling fresh versus frozen embryo transfer, which generated slightly different outcomes and therefore slightly different costs. However all of my cost estimates are within a 5% difference of theirs. In Table 8, Little et al.'s costs are presented in the first column, and the costs generated by my comparable model are in the second column.

As indicated by the asterisks under these base case conditions, my model predicts that DET is the least costly embryo transfer decision for women under 35 years; for women over 35, TET is the least costly transfer decision. These results suggest that the higher probability of per-cycle conception in the under 35 age group results in fewer average total cycles needed for women to conceive, which in turn means that women are less likely to undergo---and thereby incur the costs of---the full 5 cycles. Additionally, women in this age group are more likely to freeze their embryos and have them available

[29] Little et al.'s model includes the same short-term IVF costs as mine, but only the long-term costs of cerebral palsy and none of the other long-term complications for which I have cost estimates.

for frozen embryo transfer, which is less costly than fresh embryo transfer, and therefore figures into the lower total costs. Furthermore, because the probability of conception is very similar between SET, DET and TET for women under 35, transferring more than one embryo would not significantly alter the chance of pregnancy. On the other hand, women in the older age groups have a much lower probability of conception, so they are more likely to undergo the full 5 IVF cycles. Older women also tend to choose the more costly fresh embryo transfer procedure, further driving total costs as maternal age increases. All of these factors contribute to the pattern of increasing costs with increasing maternal age, to the point where the model predicts that the higher likelihood of conception under TET is enough to make that the least costly embryo transfer decision for older women.

These least-cost outcomes are quite similar to Little et al.'s. The 35-37 year maternal age category presents the only difference: my model predicts TET as the least costly embryo transfer decision, whereas Little et al.'s predicts DET as the least costly transfer decision. However, the cost difference between DET and TET is negligible, at about $250 in both Little et al.'s model and mine; this amount represents less than 1% of the total transfer cost. The fact that our results are flipped (i.e. that my model predicts TET as $250 less than DET, while Little et al.'s predicts DET as $250 less than TET) reflects the fact that both transfer decisions hover around the same total cost, with small uncertainties in probabilities and costs that likely allow for the overlap between the optimal decisions generated by the two models.

The third column in Table 8 presents the cost estimates generated when I incorporated costs of other long-term complications in addition to cerebral palsy, including asthma and ADL limitations. These costs do not include the long-term costs of raising a typical healthy child, but rather build directly upon Little et al.'s approach of including only the long-term costs of health complications. As is logical, all costs increased when these long-term costs were added. Furthermore, the costs of TET increased in greater proportion as compared to the costs for DET and SET; this is expected, given earlier descriptive statistics which showed that long-term complications were more prevalent in multiple gestation pregnancies. Adding these additional costs also shifted the least costly transfer decisions. Because of the increased likelihood for all of these complications when more embryos are transferred, the least costly transfer decision for women age 37 and under is SET; it is DET for women age 38 and above.

The fourth column in Table 8 presents my 18-year estimates that include costs of regular childcare. For parents who plan to only have one child, the costs of regular childcare for an additional child can be quite considerable. Not surprisingly, SET is predicted as the least costly transfer decision in all maternal age groups. This is largely due to the fact that the base costs of raising one healthy child are significantly lower as compared to the costs of raising two or three healthy children, despite some benefits of economies of scale.

Table 8: Short- and Long-Term Costs for Five Cycles of In Vitro Fertilization by Embryo Transfer Strategy and Maternal Age Group

	Parental Costs from Little et al.'s Study	Parental Costs from Base Case Model (inputs similar to those of Little et al.)	Parental Costs, with Additional Long-Term Complication Costs	Parental Costs, with ALL Long-Term Childcare Costs (Adjusted)
Women Under 35 y				
SET	26,401	26,401	32,110*	250,807*
DET	25,198*	25,747*	42,833	312,481
TET	25,350	26,163	50,288	338,425
Women 35-37 y				
SET	26,401	27,288	32,200*	229,830*
DET	25,198*	26,252	40,950	285,433
TET	25,350	26,009*	44,864	304,130

Women 38-40 y				
SET	42,042	44,052	46,983	153,559*
DET	35,720	34,389	39,193*	224,150
TET	33,185*	32,055*	45,800	266,094
Women 41-42 y				
SET	48,530	48,695	49,906	101,103*
DET	45,407	45,005	48,116*	148,348
TET	43,862*	43,199*	49,855	181,443

**indicates the least costly transfer decision*

In looking at the short-term cost trends between different maternal age groups, the increasing costs with maternal age can be explained by the higher rate of fresh embryo transfer among older women, a procedure which is more than double the cost of frozen embryo transfer. Because we are considering costs from the parental perspective, the cost of IVF---and by extension the cost difference between fresh and frozen embryo transfer---is the major short-term cost driver. However the long-term cost trends show that total costs for every embryo transfer decision decrease with maternal age. This can be explained by the fact that older women are simply less likely to conceive, as was described in the gestational outcome results previously discussed. Therefore, older women are less likely to incur the long-term costs associated with raising a child at all. The long-term costs of childcare are therefore much greater in younger age groups because younger women experience a higher rate of conception.

Cost-Effectiveness Results

<u>Short Term</u>

To get a sense of parents' short-term decision making strategy, I first looked at short-term cost-effectiveness results to determine a couple's optimal decision if they highly value their present costs and utilities.[30] To do this, I limited my model to consider only the costs and utilities associated with the IVF procedure and immediate outcome---including the disutility associated with IVF failure and the varying utilities associated with the different child health outcomes. Operating under a short-term perspective, women under age 35 would find it cost-effective to transfer two embryos at a $50,000/QALY cost-effective threshold,[31] or one embryo at a cost-effective threshold of $61,920 per QALY gained (Table 9). Women between the ages of 35 and 37 would find it most cost-effective to transfer three embryos, up to a cost-effective threshold of $281,053; if their valuation for IVF intervention exceeds $281,053 per QALY gained, they would find it most cost-effective to transfer two embryos. These women would

[30] This is a likely scenario for couples who have just learned they are infertile, as they might be emotionally overwhelmed by the reality of their health crisis.

[31] In order to make a decision, in absolute terms, as to whether or not a health intervention is "cost-effective"---in essence, worthy of funding at its level of effectiveness---a specific value for a cost-effectiveness ratio must be deemed "acceptable." However specific cutoff values are usually reflective of an individual's, group's, or institution's particular budget constraint. Therefore, it is near impossible to determine a precise and appropriate cost-effective cut-off for all couples undergoing IVF. $50,000/QALY is a value commonly cited in health economics literature as a cut-off ratio that is considered cost-effective, however many researchers would suggest that this cut-off is extremely low. For a full discussion of various incremental cost-effectiveness ratios and their interpretations, please refer to Weinstein (1995).

never find it most cost-effective to transfer one embryo, as SET is dominated (it is both more costly and less effective than either DET or TET).

For women age 38 and older, SET and DET are dominated by TET, meaning that TET is the least costly (in dollars) and most effective (in quality-adjusted life years gained) embryo transfer decision. Intuitively, this means that for women in this age bracket, any disutility from adverse pregnancy outcomes under TET is outweighed by both the higher IVF costs and the disutility from IVF failure under SET and DET.

Table 9: Short-Term Cost-Effectiveness of Different Embryo Transfer Decisions from the Parental Perspective

Strategy	Cost	Incr Cost	Effectiveness	Incr Effectiveness	C/E	Incr C/E (ICER)
Under 35 y						
DET	$ 24,800		1.8879		$ 13,148	
SET	$ 26,000	$ 1,100	1.9064	0.0186	$ 13,623	$ 61,920
TET	$ 24,800	$ -	1.8753	-0.0126	$ 13,237	(Dominated)
35-37 y						
TET	$ 24,900		1.85808		$ 13,424	
DET	$ 25,400	$ 500	1.85976	0.00168	$ 13,665	$ 281,053
SET	$ 26,900	$ 1,500	1.85868	-0.00108	$ 14,477	(Dominated)
38-40 y						
TET*	$ 31,000		1.809		$ 17,273	
DET	$ 34,000	$ 3,000	1.766	-0.043	$ 19,173	(Dominated)
SET	$ 44,000	$ 13,000	1.621	-0.188	$ 27,044	(Dominated)
41-42 y						
TET*	$ 42,800		1.626		$ 26,310	
DET	$ 44,800	$ 2,000	1.578	-0.048	$ 28,378	(Dominated)
SET	$ 48,600	$ 5,800	1.457	-0.169	$ 33,359	(Dominated)

Long Term

These short-term results take none of the various outcome utility estimates into account. The outcome utilities have a much greater impact on long-term parental quality of life, depending upon the health of their child and the 5-cycle failure or success of IVF. Furthermore, long-term costs of childcare would also figure into a couples’ cost-utility framework if they are making their embryo transfer decision with the long term in mind. The long-term cost-effectiveness results (Table 10) suggest that SET is the dominant transfer decision for women 37 and younger, being both less costly and more effective in the long-run as compared to DET or TET. This can be attributed to the fact that the simple costs of childcare increase with every additional child, and multiple gestation pregnancies are much more common under the higher embryo transfer options in these younger age groups. Because there is no additional utility assigned to having twins or triplets in this base case (a successful pregnancy results in a utility of one for all healthy outcomes regardless of the number of children born), parents would maximize their utility and minimize costs by choosing an embryo transfer decision that would most likely result in a healthy singleton birth. Furthermore, because the incremental utility decreases as more embryos are transferred, the lower utility assigned to poor gestational outcomes actually outweighs the utility loss associated with IVF failure in the long run in these younger age groups. This again can be attributed to the higher rate of multiple births and the associated complications in the younger age groups.

However the long-term results for women in the older age groups do not indicate a dominant transfer decision. In fact, at a threshold of $50,000, DET would be a cost-effective decision for women ages 41-42; at a threshold of $100,000 DET would be cost-effective for all women age 38 and over, and TET would be cost-effective for women ages 41-42; and at a threshold of $150,000, both DET and TET would be cost-effective for all women age 38 and over. For the remainder of my analysis, I will describe all of my results relative to a threshold incremental cost-effectiveness ratio (ICER) of $100,000 per QALY.[32]

[32] In order to make a decision, in absolute terms, as to whether or not a health intervention is "cost-effective"---in essence, worthy of funding at its level of effectiveness---a specific value for a cost-effectiveness ratio must be deemed "acceptable." However specific cutoff values are usually reflective of an individual's, group's, or institution's particular budget constraint. Therefore, it is near impossible to

Table 9: Long-Term Cost-Effectiveness of Different Embryo Transfer Decisions from the Parental Perspective

Strategy	Cost	Incremental Cost	Effectiveness	Incremental Effectiveness	Cost/Effectiveness (C/E)	Incremental C/E (ICER)
Under 35 y						
SET	$ 251,000		18.183		$ 13,793	
DET	$ 312,000	$ 62,000	17.919	-0.264	$ 17,438	(Dominated)
TET	$ 335,000	$ 84,000	17.745	-0.438	$ 18,883	(Dominated)
35-37 y						
SET	$ 230,000		17.705		$ 12,981	
DET	$ 285,000	$ 56,000	17.629	-0.077	$ 16,192	(Dominated)
TET	$ 304,000	$ 74,000	17.575	-0.131	$ 17,305	(Dominated)
38-40 y						
SET	$ 154,000		15.43		$ 9,984	
DET	$ 235,000	$ 81,000	16.78	1.35	$ 14,028	$ 60,168
TET	$ 276,000	$ 41,000	17.14	0.36	$ 16,108	$ 113,151
41-42 y						
SET	$ 101,000		13.85		$ 7,297	
DET	$ 148,000	$ 47,000	15.01	1.15	$ 9,884	$ 40,937
TET	$ 181,000	$ 33,000	15.44	0.43	$ 11,751	$ 76,702

Sensitivity Analyses

Because I needed to assume or estimate so many of the utility values in my long-term model, I first determined which variables in my model were most sensitive[33]; I then ran one-way sensitivity analyses on those variables. The most sensitive utility values were those assigned to IVF failure and to healthy gestational outcomes. One of the most sensitive cost variables was that assigned to long-term costs of childcare; because this estimate was also based on many assumptions, I ran a sensitivity analysis on this cost variable. I included a final sensitivity analysis that altered the relative utilities assigned to healthy singleton, twin, and triplet outcomes, respectively.

determine a precise and appropriate cost-effective cut-off for all couples undergoing IVF. $50,000/QALY is a value commonly cited in health economics literature as a cut-off ratio that is considered cost-effective, however many researchers would suggest that this cut-off is extremely low. For a full discussion of various incremental cost-effectiveness ratios and their interpretations, please refer to Weinstein (1995).

[33] I ran two Tornado diagrams using the TreeAge software---one on cost variables and the other on utility variables---in order to determine which of these variables was most sensitive in my model.

Sensitivity Analysis on IVF Failure Utility Value

Sensitivity analyses revealed that SET remained the dominant embryo transfer strategy for women under age 37, for IVF failure utilities ranging from 0.55 to 0.95. The ICERs for women age 37 and over varied with changes in the IVF failure utilities, with ratios that were lower than in the base case if the IVF failure utility was under 0.68, and greater when the IVF failure utility was over 0.68. These results would be expected, since they imply that couples whose quality of life is severely and negatively impacted by IVF failure would find it more cost-effective to transfer more embryos; couples whose quality of life is not drastically impacted by IVF failure would find it more cost-effective to transfer fewer embryos, thereby diminishing their risks for childbirth complications. Varying this utility did not significantly impact the cost-effectiveness of any of the transfer decisions until the utility value assigned to IVF failure reached 0.85, at which point neither DET nor TET fell within a $100,000 cost-effective threshold for any maternal age group (all of the specific ICERs can be found in Table A7 in the Appendix). However a utility of 0.85 seems a high value to assign to infertility, given that living with hay fever/allergies is assigned a utility of 0.87 (Gold et al., 1998); again, there is no literature on the utilities assigned to living with infertility, but it would seem that an individual's quality of life would be more severely impacted if she were not able to reproduce than if she had seasonal allergies.

Sensitivity Analysis on Healthy Child Utility Value

The other most sensitive utility value was the utility assigned to a healthy child outcome. One-way sensitivity analyses on this utility again had no effect on the transfer decision of women under age 37, as SET remained dominant even as the utility assigned to a healthy child outcome was relaxed to 0.85. However the ICER values for the older age groups did change as the utility was relaxed (specific values are available in Appendix Table A8). As would be expected, the ICER values increased as the utility assigned to a healthy outcome decreased. This demonstrates that when a couple values a healthy child outcome less and less, the costs of undergoing the IVF procedure increasingly outweigh the benefits. However there were no significant changes in cost-effective transfer decisions relative to the base case, as DET still remained cost-effective at a threshold of $100,000 for women age 37 and over even if they only assign a utility of 0.9 to a healthy child outcome; TET remained cost-effective at a threshold of $100,000 for women between the ages of 41-42 even if they only assign a healthy baby a utility value of 0.92.

<u>Sensitivity Analysis on Long-Term Childcare Cost Estimate</u>

Because my estimate for long-term childcare costs was also based largely upon assumptions, and because this cost variable was among the more sensitive cost variables in my model, I also ran a one-way sensitivity analysis on the cost of raising a healthy child. The results were similar to the sensitivity analyses on utilities, as SET remained dominant in the younger age groups and DET remained within a $100,000 cost-effective threshold for all women age 38 and over. However even TET became cost-effective at a $100,000 threshold for all women age 38 and over as the cost of raising a child decreased below $200,000 (please see Table A9 in the Appendix for the specific ICER values). The trend of the increasing cost-effectiveness of transferring multiple embryos with the decreasing cost of raising each child makes intuitive sense: as the cost to raise a child decreases, a couple's anticipated long-term costs would decrease regardless of the number of children they have. Thus, more embryos are transferred because it costs less (in the long-term) to increase the likelihood of a successful IVF procedure.

Varying Utilities of Singleton, Twin and Triplet Births, Relative to Each Other

Some studies have indicated that couples undergoing IVF have a higher desire for multiple gestation pregnancies, and would therefore obtain greater utility from a twin or triplet birth (Ryan et al., 2004). On the other hand, it has also been cited that parents of multiples live with chronic stress and fatigue and are often socially isolated, suggesting a lower quality of life for parents of multiples as compared to parents of singletons (American Society for Reproductive Medicine). I ran sensitivity analyses to gauge the effects of these hypothesized utility schemes on the long-term cost-effectiveness estimates (Table 10).

When healthy singletons were valued at U=1 and twins and triplets valued as low as U=0.85, none of the cost-effectiveness estimates changed with respect to a $100,000 cost-per-QALY cost-effectiveness threshold relative to the base case (although the ICERs themselves did change---please see the results in Table 10). Interestingly, when twins and triplets were valued at U=1, and a singleton birth was valued at U=0.9, DET was no longer dominated in any age group. However, when singletons are assigned a utility of 0.9 relative to a utility of 1.0 for twins and triplets, the cost-effective threshold would have to be nearly $500,000 per QALY gained in order for DET to be cost-effective for women under age 35. Even TET was no longer dominated in the 35-37-year age group when singletons were valued at less than one, although the cost-effective threshold would again have to be set unreasonably high for the procedure to be considered cost-effective (at $881,620 if singletons were valued at 0.9 and $318,333 if singletons were valued at 0.85---all results are reported in Table 10).

Keep in mind, however, that the utility assigned to having a child with an ADL limitation is 0.91. So, in order for any of the low-value singleton scenarios to play out, a couple would need to assign a higher utility to having twins with ADL limitations as compared to a having a healthy singleton child. Such a situation seems highly unlikely; but if it is the case, then TET might be cost-effective for that couple in the long term, if they have an exorbitantly high cost-effective threshold per life year gained.

Table 11: Long-Term ICERs while Varying Child Outcome Utilities

	Utility Values: Singleton=1.00 Twin=0.95 Triplet=0.90	Utility Values: Singleton=1.00 Twin=0.85 Triplet=0.85	Utility Values: Singleton=0.90 Twin=1.00 Triplet=1.00	Utility Values: Singleton=0.85 Twin=1.00 Triplet=1.00
Women Under 35 y				
SET				
DET	Dominated	Dominated	491,589	194,912
TET	Dominated	Dominated	Dominated	Dominated
Women 35-37 y				
SET				
DET	Dominated	Dominated	230,080	138,716
TET	Dominated	Dominated	881,620	318,333
Women 38-40 y				
SET				
DET	64,160	73,975	77,919	91,402
TET	142,417	214,477	125,111	132,092
Women 41-42 y				
SET				
DET	41,489	42,640	57,482	72,039
TET	87,700	118,249	87,305	93,788

Review of Major Findings

My model suggests that a patient's most cost-effective transfer decision varies based upon whether short- or long-term costs and utilities are considered; the most cost-effective transfer decision also varied by maternal age. Operating under a short-term perspective, couples <35 years would find it most cost-effective to transfer two or one embryo, depending on their cost-effective threshold. Couples 35-37 years old would most likely transfer three embryos, and parents 38 years and older would always transfer three embryos in the short term.

Operating under a long-term perspective, parents <37 years would usually find it most cost-effective to transfer a maximum of one embryo. If these younger parents place a high value on multiples over a singleton and have a high cost-effectiveness threshold, they might transfer two embryos in the long-term. Parents age 38 and older would likely transfer two or three embryos in the long-term, depending on their cost-effectiveness threshold.

My results indicate that as maternal age increases, it becomes more cost-effective to transfer more embryos in the both the short- and long-term. My results also demonstrate that parents who consider only short-term costs and outcomes would transfer more embryos as compared to parents who take into account all of the long-term costs and quality of life considerations associated with a transfer decision and its outcomes.

Conclusion

Coping with infertility is one of the most difficult realities faced by one in eight American couples (RESOLVE). Upon discovering their infertility, couples are often overwhelmed by feelings of loss and disappointment, sensing that their wishes for a family can never be fulfilled. At the same time, they are faced with the possibility of reversing their childless fate through medical treatment. Given their fragile emotional states, in addition to the incredible financial burden associated with infertility treatments, infertile couples are particularly susceptible to discretionary decision-making when choosing the number of embryos to transfer per cycle of IVF. Despite high risks for adverse child outcomes, patients often choose to transfer multiple embryos per procedure to ensure that at least one embryo develops to term. However the resulting adverse child health outcomes ultimately impact long-term parental quality of life and childcare costs. Parents may not give equal weight to these long-term effects when they are faced with the possibility of reversing their infertility, discounting long-term costs in favor of increasing their likelihood of pregnancy by transferring a high number of embryos. The goal of this paper was to determine the optimal IVF embryo transfer decision for infertile couples, and to examine the difference between the long-term and short-term cost-effective decisions. The optimal decisions were measured as those that were cost-effective from the couple's perspective, with costs captured in dollars and effectiveness captured in QALYs.

The results suggest that younger couples (age 37 and below) may not be informed of the relative costs and probabilities of pregnancy if they choose to transfer more than two embryos at a time. If they are operating under a short-term horizon, then my model suggests it would be most cost-effective for them to transfer up to two embryos at a time. If they are operating under a long-term horizon, it would be most cost-effective for them to transfer a maximum of one embryo. Therefore, if a young couple chooses to transfer more than one embryo, it would seem that they are heavily discounting the long-term costs and utilities associated with transferring that many embryos, in favor of the short-term outcomes. Intuitively, this means that couples are more heavily weighting the short-term value of becoming pregnant in comparison to the long-term costs associated with those pregnancy outcomes.

The results further suggest that older couples (age 38 and above) might find it cost-effective to transfer two or more embryos if they are operating under a long-term perspective, depending upon their cost-effectiveness thresholds for the IVF procedure. If these older parents only account for short-term considerations, it would always be most cost-effective for them to transfer three embryos. Under a long-term horizon and assuming parents would be equally happy with any healthy gestational outcome, couples between the ages of 38-40 would transfer two embryos at a $100,000 cost-effective threshold (assuming they are fully informed of their costs and probable gestational outcomes). Again, if they do choose to transfer more embryos, it would suggest that the couple is heavily discounting the long-term costs associated with gestational outcomes in favor of the short-term values they assign to a successful pregnancy. However, under these same conditions (long-term perspective, a $100,000 cost-effective threshold, and assigning equal value to any healthy gestational outcome), parents over age 40 would transfer up to three embryos.

The fact that the most common IVF procedures for all maternal age groups involve the transfer of at least two or more embryos[34] suggests that couples may not be fully considering---or are not fully informed of---the long-term costs and probabilities of various gestational outcomes under the different embryo transfer options. If they were, they would make more cost-effective embryo transfer decisions. Therefore, these results

[34] According to the 2002 ART Surveillance Report data, the majority of ART procedures involved transfer of more than one embryo: “Among women aged <35 years, 95% of procedures involved transfer of two or more embryos, and 53% involved transfer of three or more embryos. For women aged >42 years, 85% involved transfer of two or more embryos, and 65% involved transfer of three or more embryos” (Wright et al., 2005).

suggest that health care providers should take extra efforts to educate patients about the gestational outcome probabilities associated with IVF, emphasizing the greater likelihood of adverse child outcomes with multiple-embryo transfer. Furthermore, patients should be provided with literature outlining and comparing the long-term costs and quality of life associated with caring for multiple children and children who are mentally and/or physically disabled.

There are additional insurance-related implications of these results. Most insurers classify infertility treatments as "medically unnecessary," and therefore do not provide coverage for them; only fifteen states currently require insurers to provide some sort of coverage. At first glance this may seem a logical approach for insurers, as IVF often amounts to over $10,000 per treatment cycle. However, insurers do provide coverage for adverse pregnancy outcomes, which are more common in the multiple births associated with high-embryo transfer IVF. The healthcare costs per family of multiple-birth deliveries by ART range from $58,865 for twins to upwards of $281,698 for quadruplets (ESHRE, 2000), compared to an average of $8,674 for a singleton ART birth (Van Voorhis et al., 1998).

Interestingly, it has been shown that in states where insurers are required to cover ART treatment, women are less likely to transfer multiple embryos per IVF treatment cycle than in states without insurance coverage (Reynolds et al., 2003). This is not surprising if one assumes that women are less likely to transfer multiple embryos per IVF cycle if they can undergo the procedure a second time without concern about payment. Researchers hypothesize that because their pregnancy success is not contingent upon a single IVF cycle, couples do not feel the need to implant as many embryos to ensure a successful pregnancy---the couples are more willing to accept the risk of a failed procedure. As a result, researchers conclude that women implant fewer embryos and have fewer multiple births when insurance covers their IVF treatments. This finding goes hand in hand with the results of this paper, which show that parents overvalue short-term IVF success, largely due to the fact that costs and utility loss associated with IVF failure are overwhelming in comparison to the seemingly distant long-term costs of poor child outcomes---which in reality are much greater in magnitude. If insurance covered the cost of IVF, the total costs and utility loss associated with the risk of IVF failure could be decreased because patients could undergo the procedure as often as desired at no monetary cost. By decreasing the short-term costs, patients would give long-term and short-term costs more equal weight when deciding how many embryos to transfer, which may ultimately lead to more cost-effective parental decision-making.

While this study did generate very interesting and informative results---both in line with what has been shown in previous literature and what is observed in the real world---it does have its limitations. I was not able to reproduce the complex modeling of fresh versus frozen embryo transfer that Little et al. did in their study. While this did not seem to severely affect the outcome results generated by my model, my numbers were not perfectly in line with those predicted by Little et al.'s model. Additionally, I did not introduce any method of assigning costs or utility values to leftover frozen embryos: ethical considerations may impact utility estimates associated with freezing, destroying, or donating those embryos[35] and there are often additional costs associated with continual cryopreservation (Gurmankin et al., 2007).

[35] According to researchers, the moral status of excess embryos produced at IVF clinics is "highly controversial," often a topic of "ethical divergence" (Garumpkin et al., 2007). Because of this, leftover

Furthermore, my model only considers a single attempt at a successful gestational outcome. In the real world, couples will often undergo many successful IVF procedures because they desire to have more than one child, but only a single child at a time. However previous births might affect the utilities assigned to IVF failure or success by maternal age, depending upon how many children a couple already has. My model is also limited in its capability of assigning sufficient utility to additional children, because it assumes that any successful gestational outcome is equal to one, and does not allow for each child born to be assigned a utility of one because total utility is assigned on a zero to one scale. Therefore, because successful pregnancy is the optimal outcome regardless of the number of children involved, the additional utility from a second child cannot be captured and might therefore be outweighed by the additional costs of that second child. However I did attempt to reconcile this utility problem in my sensitivity analyses, where I allowed for a healthy singleton gestational outcome to equal a utility less than one; I then assigned multiples a higher utility value than singletons, to capture the additional utility for the second and/or third child.

Because the literature on utilities is limited, and because the 18-year projected costs of childcare are truly estimates culled from a literature review, some of my cost data and most of my utility data are merely well-reasoned approximations, as described in the data section. Because they are estimates, these data may skew my results (although I am unsure which way they would be skewed, since they are truly well-reasoned estimates). To account for the lack of an IVF failure utility published in the literature, I made a logical estimate for the utility value by maternal age group, and then further tested the

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embryos might cause uncalculated disutility to parents who might become morally alarmed at the thought of destroying their remaining embryos, or who might come under social or religious attack for donating their excess embryos for scientific research.

range of that utility value in sensitivity analyses. Despite my best efforts, these data limitations might lead some to question the reliability of my results. Additionally, because the data are based on population averages, the results of this analysis may not apply to every couple making infertility treatment decisions. As is often said, “ART is truly an Art.”

Ultimately, the cost-effectiveness estimates generated by my model are convincing in their ability to explain real-world decision making. Furthermore, it is not unreasonable to think that couples presented with the crisis of infertility might discount long-term costs in favor of the easiest road to a short-term “fix.” It is common human behavior to place more weight on immediate utility and discount future costs. It would be even more reasonable to suspect such behavior during a stressful period in a couple’s life, when they would be very eager to resolve their infertility problem. The results of this study could be very useful in demystifying IVF options for couples looking into infertility treatment, helping them to make decisions that will lead to many years of happy, healthy family life.

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APPENDIX

Table A1: Probability that a Woman would be able to Freeze a Given Number of Embryos, by Maternal Age Group (as reported in Little et al., 2006)

	Maternal Age (years)			
Number of Frozen Embryos	Under 35 y	35-37 y	38-40 y	41-42 y
1	0.90	0.82	0.76	0.53
2	0.71	0.69	0.63	0.42
3	0.64	0.56	0.50	0.30
4	0.51	0.42	0.37	0.18
5	0.38	0.29	0.24	0.07

Table A2: Initial IVF Treatment Cycle Costs

	Cost	Source
IVF Cycle, 2006	$12,400	American Society for Reproductive Medicine (2003)
Lost parental work time (assumes both partners miss one week of work)	80 hours	Neumann et al. (1994)
Hourly Wage (Dec2006)	$17.05/hour	US Department of Labor, Bureau of Labor Statistics
Total Lost Wages per Couple	$1,364	
Total Cost per IVF Procedure	$13,764	

Table A3: Maternal Complications, According to the Number of Fetuses

Complication	Singleton	Twins	Triplets	Source
C-Section Delivery rate	26.1%	57%	89.5%	ESHRE Capri Workshop (2000)
Premature Rupture of Membranes	26.1%	57.0%	89.5%	
Rate of Toxaemia	4.8%	8.3%	11.0%	
Antenatal Maternal Hospitalization rate	12.2%	30.5%	56.9%	
Gestational Diabetes Mellitus		3.1%	38.5%	Seoud et al. (1992)
Rate of pregnancy-induced hypertension		17%	38.6%	

In all cases, $p < 0.001$

Table A4: Adjusted Odds Ratios for Maternal Complications and Pregnancy Outcomes, by Maternal Age Group

	32-34 years*	35-37 years*	38-39 years*	40-42 years
Maternal Complications[#]	1.00	1.11	1.13	1.28
Premature Birth (<32 weeks gestation)	1.00	1.23	1.31	1.65
Infant Death	1.00	1.18	1.27	1.36

Table A5: Miscarriage Data

Treatment	Cost (You & Chung, 2005)	Incidence (Butler et al., 2005)	Cost x Incidence
Expectant Care	$1172	0.81	$949.32
Surgery	$2007	0.19	$381.33
TOTAL Cost per Miscarriage			$1330.65

Table A6: Long-Term LBW and ELBW Outcomes, Measured at 8 Years of Age

Outcome	Rate	Source
Limitation in more than one ADL (<1500g)	40%	McCormick (1991)
Limitation in more than one ADL (1500-2500g)	27%	
Asthma (<1500g)	18%	
Asthma (1500-2500g)	12%	

Table A7: ICER Values for Sensitivity Analysis on Utility Assigned to IVF Failure

Transfer Strategy	ICERs for Different Utility Values Assigned to IVF Failure						
	0.55	0.6	0.65	0.7	0.75	0.85	0.95
Under 37 y							
SET							
DET	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TET	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
38-40 y							
SET							
DET	$ 40,174	$ 46,061	$ 53,970	$ 65,157	$ 82,195	$ 172,132	(Dominated)
TET	$ 69,407	$ 81,532	$ 98,785	$ 125,300	$ 171,271	$ 643,348	(Dominated)
41-42 y							
SET							
DET	$ 29,956	$ 34,116	$ 39,617	$ 47,233	$ 58,475	$ 111,597	$ 1,219,006
TET	$ 52,945	$ 61,620	$ 73,696	$ 91,657	$ 121,194	$ 340,935	(Dominated)

Table A8: ICER Values for Sensitivity Analysis on Utility Assigned to a Healthy Child Outcome

Transfer Strategy	ICERs for Utilities Assigned to Birth of a Healthy Child			
	0.85	0.9	0.95	1
Under 37 y				
SET				
DET	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TET	(Dominated)	(Dominated)	(Dominated)	(Dominated)
38-40 y				
SET				
DET	$ 111,658	$ 86,877	$ 71,097	$ 60,168
TET	$ 204,399	$ 161,095	$ 132,933	$ 113,151
41-42 y				
SET				
DET	$ 72,928	$ 57,857	$ 47,948	$ 40,937
TET	$ 130,960	$ 105,972	$ 88,992	$ 76,702

Table A9: ICER Values for Sensitivity Analysis on Costs of Raising a Healthy Child

Transfer Strategy	ICERs for Different Costs of Raising a Healthy Child				
	$ 100,000	$ 150,000	$ 200,000	$ 250,000	$ 300,000
Under 38 y					
SET					
DET	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
TET	(Dominated)	(Dominated)	(Dominated)	(Dominated)	(Dominated)
38-40 y					
SET					
DET	$ 24,909	$ 37,777	$ 50,646	$ 63,514	$ 76,383
TET	$ 51,270	$ 73,854	$ 96,439	$ 119,023	$ 141,608
41-42 y					
SET					
DET	$ 16,351	$ 25,324	$ 34,297	$ 43,270	$ 52,243
TET	$ 34,455	$ 49,873	$ 65,292	$ 80,711	$ 96,129