Markov modeling of vasectomy reversal and ART for infertility: how do obstructive interval and female partner age influence cost effectiveness?

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Objective: To apply Markov models to assess the cost effectiveness of the relative impact of obstructive interval and female partner age on fertility using either assisted reproductive technology (ART) or vasectomy reversal, and elucidate the impact of these variables on fertility.

Design: Markov models based on review of published literature and available ART outcome data.

Setting: University-based clinical practice.

Patient(s): Simulation runs of 50,000 patients for each analysis.

Intervention(s): Varying vasectomy obstructive interval and maternal age.

Main Outcome Measure(s): Cost effectiveness, willingness to pay (WTP), and net health benefit.

Result(s): Base case analysis showed ART yields a higher pregnancy rate and higher cost than vasectomy reversal. Sensitivity analysis showed female age has a greater effect on cost effectiveness than obstructive interval. At a WTP < $65,000, vasectomy reversal is more cost effective than ART. With increasing WTP, ART is more cost effective over wider windows of female age.

Conclusion(s): Markov modeling of fertility after vasectomy suggests female age has more impact than vasectomy obstructive interval on cost effectiveness. (Fertil Steril® 2007;88:840–6. ©2007 by American Society for Reproductive Medicine.)

Key Words: Markov process, decision analysis, cost effectiveness, assisted reproductive technology, vasectomy reversal

It is estimated that over 800,000 vasectomies are performed annually in the United States (1). In addition, 3% to 8% of men seek future fertility after the procedure (1). Vasectomy reversal and assisted reproductive technology (ART) are both used to treat male infertility resulting from vasectomy. In 2004, over 110,000 ART procedures were reported to the Centers for Disease Control and Prevention, some of which were performed for vasectomy-induced infertility (2). With an average cost of $12,400 per in vitro fertilization (IVF) cycle (3), ART is clearly a costly option. Although vasectomy reversal can be less costly in many instances, many reproductive endocrinologists routinely recommend ART to couples with vasectomy-associated infertility.

Randomized, controlled clinical trials to determine the optimal treatment for vasectomy-associated infertility have not been undertaken, nor are they considered feasible. In addition, few cost-effectiveness studies exist to help physicians and patients make appropriate decisions regarding infertility treatment after vasectomy (4–6). In such instances, decision modeling can be very helpful in dissecting out relevant and significant variables that impact a clinical condition.

Decision analytic models are methods of estimating and calculating outcomes by identifying the clinical question, disaggregating the problem into discrete units to include all reasonable choices and consequences, and assigning probabilities and costs to the various events and outcomes (7). Based on our prior work with decision analysis modeling of ART versus vasectomy reversal, we observed that vasectomy reversal is often more cost effective than ART, but the variable of vasectomy reversal patency, and indirectly vasectomy obstructive interval, is an important determinant of cost effectiveness (6). In addition, we assumed that female fecundity, and hence female age, was independent of treatment modality. Clinically, the decision to choose vasectomy reversal or ART is more complex in the setting of the "older" vasectomy (obstructive interval >14 years) or with advanced maternal age (>38 years old). Indeed, the relative impact of these clinical variables is very real to the many couples affected by them.

To our knowledge, the literature has not yet examined the combined effects of obstructive interval and female partner age with time on the success of fertility treatment options after vasectomy. Thus, we felt an analysis of these two clinical variables *over time*, through Markov modeling,

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would provide important additional information regarding the cost effectiveness of vasectomy reversal versus ART after vasectomy.

Markov modeling is a form of decision analysis in which hypothetical patients proceed through health states overtime based on pre-defined probabilities and costs (7). As patients are cycled, outcomes, including incurred costs and events, are tracked. Male infertility resulting from vasectomy is suitable for this form of analysis because the condition entails discrete states (i.e., obstruction or patency) which can change with time as interventions are performed.

Although decision modeling has suggested that vasectomy patency rate and maternal age are relevant variables that drive the cost effectiveness of treatments for vasectomy-induced infertility (6), how these variables interact to influence outcomes over time is unclear. Therefore, to better understand the relative impact of obstructive interval and female partner age on fertility after vasectomy, we applied Markov models to compare the cost effectiveness of ART versus vasectomy reversal.

MATERIALS AND METHODS

Model Design

For this study, Markov models were created for infertile men seeking paternity with postvasectomy obstruction (Fig. 1). The decision tree compared initial ART versus vasectomy reversal. After two failed vasectomy reversals, the latter arm crossed over to ART. The interval between a second failed vasectomy reversal attempt and cross-over to ART was 1 year. Failed ART led to further ART attempts, with cycles performed every 3 months as needed. The interval for a second vasectomy reversal attempt, if needed, was 1 year.

Markov model design and cost-effectiveness analyses were performed using the TreeAge Pro software suite with the Healthcare module (www.treeage.com).

Cohort Size and Time Horizon

We simulated 50,000 hypothetical patients in each treatment arm until pregnancy was achieved or for 3 years, whichever came first.

Model Assumptions

Although there is no literature that specifically addresses this issue, we made the conservative assumption that pregnancy rates after vasectomy reversals with obstructive intervals <15 years are 10% higher than those for obstructive intervals >15 years (8). We assumed that infertility in men was due solely to obstruction, and that failure of pregnancy after reversal was not the result of nonazoospermic failure. For patients who crossed over from vasectomy reversal to ART, costs for ART were assumed to be the same whether or not the vasa were patent after vasectomy reversal. We also assumed that pregnancy rates after subsequent IVF cycles and vasectomy reversals were the same as those after initial IVF cycles and vasectomy reversals (i.e., no decrement with successive treatments).

Probability Values

Outcome probabilities applied to the model were derived from published sources whenever possible. Other outcomes were procured from institutional sources. A list of all relevant outcomes is given in Table 1.

Base Case Values and Analysis

"Base case" analysis refers to running Markov models with a set of chosen baseline values for variables.

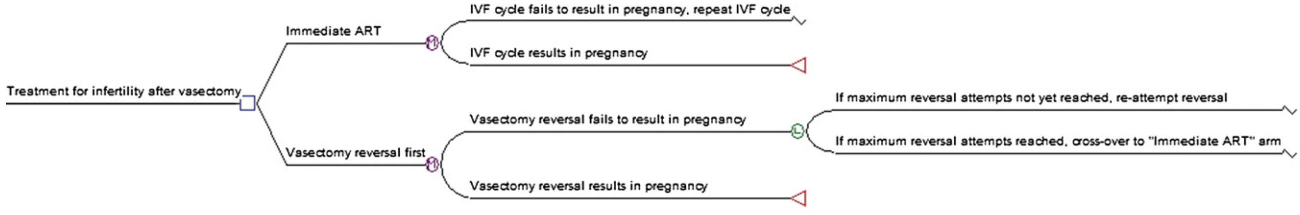
Cost-effectiveness Analysis

"Costs" were equated with out-of-pocket costs for patients. Costs of interventions were calculated from national averages and institutional costs (see Table 1). "Effectiveness" was defined as clinical pregnancy. Each hypothetical patient achieving pregnancy received an effectiveness score of 1, whereas patients failing to achieve pregnancy received an effectiveness score of 0. Hence, "cost effectiveness" was defined as the ratio of out-of-pocket costs to pregnancy rate, with lower ratios being more desirable.

By definition, if one treatment option is more effective but more costly than another option, both options are equally cost effective. Subsequently, cost effectiveness was referenced

FIGURE 1

Markov model for immediate assisted reproduction versus vasectomy reversal protocols for male infertility after vasectomy.



Hsieh. Markov models of vasectomy reversal and ART. Fertil Steril 2007.

TABLE 1

Costs, values, and outcome probabilities for base case analysis, and clinical parameter value ranges and threshold values from sensitivity analysis.

Row	Variable	Base case value	Source of evidence for base case value	Range for sensitivity analysis	Threshold value(s)[a]
1	Costs per IVF cycle	$12,400	2004 SART National Summary	0-$20,000	<$14,000
2	Costs per vasectomy reversal	$8,500	2006 UCSF institutional costs	0-$16,000	>$7,000
3	Obstructive interval	14 years	2006 UCSF institutional average	0-20 years	None
4	Female partner age	34 years	2006 UCSF institutional average	25-50 years	33.0 to 33.6
5	Interval for vasectomy reversal or cross-over to ART	12 months	2006 UCSF institutional practice	6-24 months	>7.8
6	Maximum number of vasectomy reversals	2	2006 UCSF institutional practice	1-3	None
7	Interval for IVF cycles	3 months	2006 UCSF institutional practice	1-6 months	None
8	Time limit for pregnancy to occur	36 months	2006 UCSF institutional average	12-60 months	<52.2
	Probability of pregnancy, per IVF cycle,				
9	female partner age <35 years	42.2%	2004 SART National Summary	0-100%	>60%
10	35–37 years	35.4%	2004 SART National Summary	[b]	n/a
11	38–40 years	26.4%	2004 SART National Summary	[b]	n/a
12	>40 years	17.1%	2004 SART National Summary	[b]	n/a
	Probability of pregnancy after vasectomy reversal,				
13	obstructive interval <15 years, female age <30 years	74%	Large retrospective reviews (8, 17) and expert opinion	[b]	n/a
14	obstructive interval <15 years, female age 30-35 years	59%	Large retrospective reviews (8, 17) and expert opinion	0-100%	<40%
15	obstructive interval <15 years, female age 36-40 years	42%	Large retrospective reviews (8, 17) and expert opinion	[b]	n/a
16	obstructive interval <15 years, female age >40 years	38%	Large retrospective reviews (8, 17) and expert opinion	[b]	n/a
17	obstructive interval >15 years, female age <30 years	64%	Review of 127 patients (17)	[c]	n/a
18	obstructive interval >15 years, female age 30–35 years	49%	Review of 127 patients (17)	[c]	n/a
19	obstructive interval >15 years, female age 36–40 years	32%	Review of 127 patients (17)	[c]	n/a
20	obstructive interval >15 years, female age >40 years	28%	Review of 127 patients (17)	[c]	n/a

[a] Threshold indicates variable value(s) at which the immediate ART treatment protocol becomes more cost-effective at a willingness-to-pay of $100,000. For example, "<$10,000" indicates that at less than $10,000 for a given cost, the immediate ART protocol is more cost-effective.

[b] Age ranges for parameter (see second column) do not include base case age, hence one-way sensitivity analysis was not performed.

[c] Obstructive interval ranges for parameter (see second column) do not include base case obstructive interval, hence one-way sensitivity analysis was not performed.

Hsieh. Markov models of vasectomy reversal and ART. Fertil Steril 2007.

against willingness-to-pay (WTP), which represents the highest increase in costs that patients are willing to pay per unit increase in pregnancy rate.

Net Health Benefits

Net health benefit (NHB) is calculated for a treatment protocol using associated costs and effectiveness as well as WTP, under a given set of values for clinical parameters. The formula is as follows:

$$\text{Net health benefit} = \text{Effectiveness} - (\text{Costs}/\text{Willingness to pay})$$

Thus, a higher NHB for a treatment option indicates higher cost effectiveness. For this Markov model, effectiveness is equated with clinical pregnancy rate.

Sensitivity Analysis

Sensitivity analysis refers to the analytic process by which one or more variables are altered while keeping other variables unchanged (i.e., at base case values) to determine which variables impact the Markov model. One-way sensitivity analyses were performed by calculating the thresholds at which a given value for a variable would change the treatment protocol that was deemed most cost effective (less costly for a higher pregnancy rate). Two-way sensitivity analysis was also performed, where two variables are varied simultaneously and thresholds are measured.

RESULTS

Base Case Example

A hypothetical patient who underwent vasectomy 14 years ago (see Table 1, row 3) presents for infertility treatment. His female partner is 34 years old (see Table 1, row 4). The couple starts in the vasectomy reversal treatment arm, and the man undergoes vasectomy reversal (see Table 1: row 14: 59% probability of success; row 2: cost of $8,500).

The vasectomy reversal fails, and he undergoes a second vasectomy reversal attempt 1 year later. The second attempt (59% probability of success, cost $8,500) also fails. One year later, the couple crosses over to ART. The first IVF cycle (see Table 1, row 10: 35.4% probability of success because female partner is now 36 years old; row 1: cost of $12,400) fails to result in pregnancy, and 3 months later, a second cycle (35.4% probability of success, cost $12,400) results in pregnancy. The couple incurs a total cost of $41,800 for these treatments, and receives an effectiveness score of 1.

Base Case Analysis

Base case analysis showed that immediate ART results in a higher overall pregnancy rate (99.4 % vs 95.3%) but incurs higher costs than vasectomy reversal (Table 2). Hence, at base case values and assuming an unlimited WTP, immediate ART and vasectomy reversal are both cost effective.

TABLE 2

What it takes to get pregnant: base case incurred costs and outcomes after 3 years of treatment.

	Immediate ART	Vasectomy reversal first
Mean costs	$31,399	$29,274
Cumulative pregnancy rate	99.4%	95.3%
Mean number of IVF cycles	2.5	1.6
Mean number of vasectomy reversals	0	1.17

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Sensitivity Analysis

One-way sensitivity analysis was performed on all variables used in the Markov model. Sensitivity analysis showed that female partner age affected cost effectiveness more profoundly than obstructive interval. This is illustrated in Figure 2 (tornado diagram).

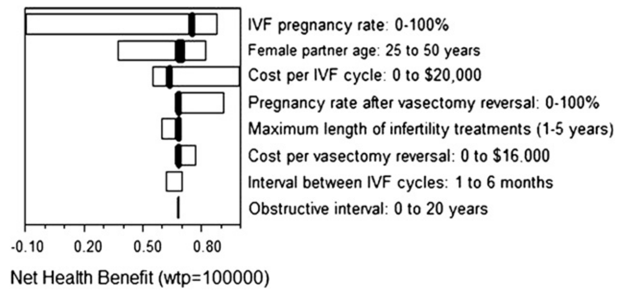
At a defined WTP of $100,000, these two variables were varied independently to examine which one more strongly affected NHB. When female partner age was varied from 25 to 50 years, the NHB for the most cost-effective protocol, vasectomy reversal, varied from 0.82 to 0.38. When female age was held constant and obstructive interval varied from 0 to 20 years, the NHB for vasectomy reversal varied much less, from 0.681 to 0.683. Because female partner age influenced cost effectiveness much more than obstructive interval, we performed subsequent NHB analyses using female partner age.

Other clinical parameters also influenced cost effectiveness of vasectomy reversal versus ART (see Fig. 2, Table 1). At a WTP of $100,000, IVF pregnancy rates influenced NHB more than any other clinical parameter. For example, NHB ranged from -0.09 to 0.88 when the IVF pregnancy rate was varied from 0 to 100%. When IVF pregnancy rates were >60%, ART became more cost effective than vasectomy reversal.

Additional clinical parameters with significant impact on cost effectiveness included costs per IVF cycle and vasectomy reversal, pregnancy rates after vasectomy reversal, the length of time that hypothetical couples spent on infertility treatment, and the interval between IVF cycles. Of these clinical parameters, all featured threshold values (see Table 1 for exact values) except for the interval between IVF cycles. It is interesting that, for a WTP of $100,000, varying the maximum number of reversal attempts from one to three (two

FIGURE 2

Tornado diagram of female partner age, obstructive interval, and other clinical parameters. Widths of horizontal bars indicate magnitude of impact of varying a parameter on net health benefits (NHB). The wider the bar, the greater the impact on NHB. Thick vertical bars indicate threshold values at which vasectomy reversal and assisted reproduction switch being more cost effective. (Exact threshold values are shown in Table 1.)



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attempts were used for base case analysis) did not make the IVF arm more cost effective than the vasectomy reversal arm.

We performed additional sensitivity analyses by testing lower vasectomy reversal success rates for obstructive intervals of <14 years (younger) when compared with >14 years (older) (data not shown). Our original assumption was that "older" vasectomy reversals had a 10% lower associated pregnancy rate than "younger" vasectomy reversals. However, when this difference in success rate was increased to 36% (the maximum possible value given that the pregnancy rate after "younger" vasectomy reversals with female partners <30 years is 64% [see Table 1]), female partner age continued to exert a greater impact on cost effectiveness than obstructive interval.

At a WTP of up to $65,000, assuming that patients were willing to pay up to $65,000 to obtain a pregnancy, vasectomy reversal was more cost effective than ART (Fig. 3). With increasing WTP, assuming that couples were willing to spend more than $65,000 for a pregnancy, immediate ART became more cost effective; this was true over wider windows of female partner age. For example, at a WTP of $100,000, vasectomy reversal was more cost effective when the female partner age ranged between 33.1 and 38.0 years. When WTP is increased to $150,000, vasectomy reversal was more cost effective when the female partner age ranged between 32.6 and 39.3 years.

Two-sensitivity analysis showed that particular combinations of clinical parameters interacted to influence cost effectiveness. For instance, female partner age interacted with costs of IVF and vasectomy reversal (data not shown). Likewise, IVF pregnancy rates interacted with these same clinical parameters to determine cost effectiveness (data not shown). Importantly, vasectomy reversal was more cost effective over most combinations of parameter values.

DISCUSSION

The success of ART for treating female infertility has led to its empirical use in cases of surgically treatable forms of male infertility, including vasectomy-associated infertility. Despite its wide acceptance, it has become clear that ART treatment is costly (9–11) and carries risks of associated complications for potential mothers as well as offspring (12, 13). In addition, there is little hard evidence to guide clinical decision-making regarding vasectomy reversal versus ART in cases of older (>14 years) vasectomies with advanced (>38 years) maternal age. Given the lack of randomized controlled trials addressing this issue, we have applied the tools of decision science to investigate the relevant issues on this topic (6).

In this study, we extend our prior work with decision modeling to further examine the cost-effectiveness issues that surround the management options for vasectomy-associated infertility. Markov modeling, unlike decision analysis, provides the added benefit of analyzing cost effectiveness of infertility treatments over time. This type of modeling provides a more realistic framework for clinicians to counsel patients using clinically apparent, patient-specific information such as female partner age, obstructive interval, and WTP. In general, we observed that when cost effectiveness is considered over time, female age (and indirectly female reproductive potential) has a greater influence than vasectomy obstructive interval on outcomes. Many infertility clinicians have long suspected this empirically, but this study provides quantitative support for this hypothesis.

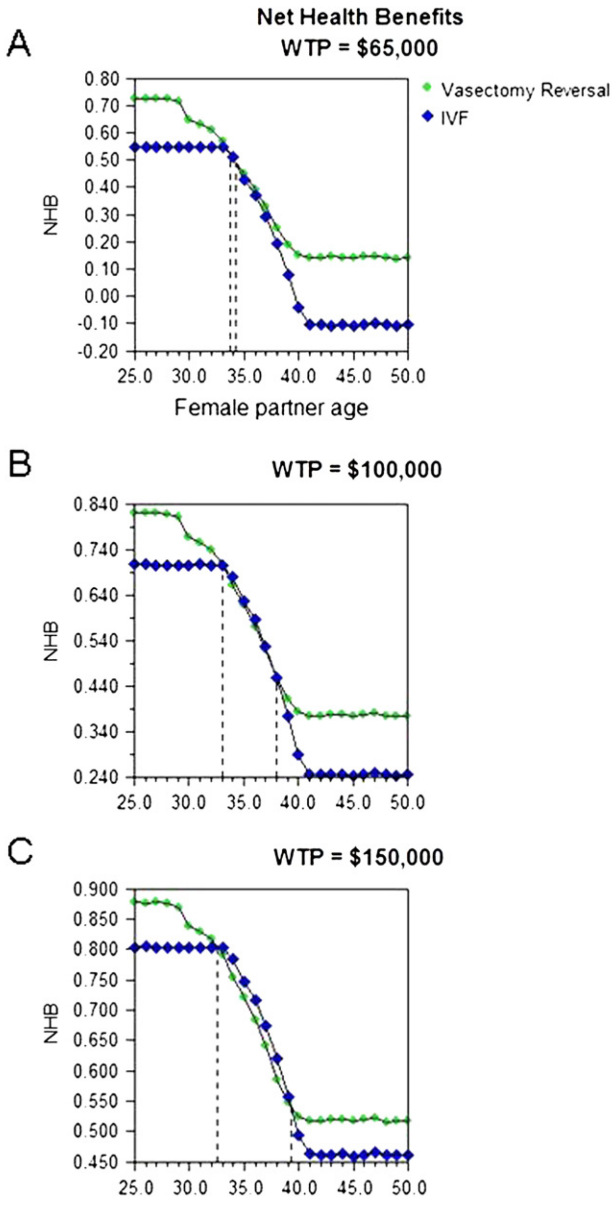
Our findings concerning patient willingness to pay are also informative. It is well recognized that patients have ceiling values for WTP for elective medical procedures, including emotionally sensitive therapies such as infertility treatment (14, 15). In 1995, Granberg et al. (15) surveyed infertile couples at two Swedish IVF clinics, and 55% of couples reported a WTP of 10,000 pounds, the equivalent of US$14,757. From this work, it was also clear that WTP for infertility treatments varied widely, and socioeconomic factors that contributed to those findings in 1995 may not apply today.

Neumann and Johannesson (14) showed that, depending on the methodology used for calculations, WTP for infertility treatment among surveyed Americans ranged from $40,640 to $63,896 for a hypothetical pregnancy rate of 100%. Applying these findings to the current study, it is interesting to note that previously reported WTP are lower than the WTP ($65,000) needed for the vasectomy reversal protocol to be more cost effective than immediate IVF. This implies that for most infertile couples, vasectomy reversal may be more cost effective.

The one-way sensitivity analysis of the variables used in our Markov models showed that clinical parameters such as female partner age, IVF and vasectomy reversal costs and pregnancy rates, the interval between IVF cycles, and the length of time spent on infertility treatments all profoundly affect cost effectiveness. Furthermore, two-way sensitivity analysis showed that female partner age interacted with IVF and vasectomy reversal costs to determine cost effectiveness. Of these clinical parameters, only female partner age and length of time spent on treatment are strictly patient specific. It is interesting that obstructive interval had little effect on cost effectiveness. However, it must be recognized that costs and pregnancy rates vary greatly among individual practices and geographic locations, and although we did not examine costs as a primary end point in this study, our models can be customized to determine optimal treatment algorithms for individual infertility centers.

FIGURE 3

Net health benefits for initial ART versus vasectomy reversal as a function of female partner age at a willingness-to-pay of (**A**) $65,000, (**B**) $100,000, and (**C**) $150,000. The vertical dotted lines indicate the female age at which the most cost-effective treatment changes from one treatment to another.



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Decision analysis models have intrinsic limitations. We chose pregnancy rates rather than live birth rates for as our outcome measure largely because the former has been reported more widely in the vasectomy reversal literature. Multiple births can significantly increase costs associated with IVF. However, to simplify the model, we did not include the consideration of multiple gestations/births. We believe that because [1] the economic perspective of our analysis was out-of-pocket costs for patients, [2] multiple births are covered by insurance, and [3] the costs of raising multiple children are postprocedural issues, it was reasonable to exclude multiple gestations from our models.

We assumed that infertility in these men was due solely to obstruction, and that failure of pregnancy after reversal was not the result of nonazoospermic failure. Furthermore, we did not factor in costs of sperm retrieval at time of reversal or for IVF/intracytoplasmic sperm injection, because we attempted to use national level data whenever possible and costs and success rates vary widely according to clinical practices. We assumed that, after a first reversal attempt, subsequent attempts would have the same success rates. When we tested the effects of a 10% decrement in success of subsequent reversal attempts (8), the cumulative pregnancy rate for the vasectomy reversal arm dropped from 95.3% to 94.1% in base case analysis (data not shown). The windows of female age in which IVF was more cost effective remained essentially unchanged despite a 10% decrement in success of subsequent reversal attempts. Hence, a realistic decrease in subsequent reversal attempt success rates did not alter cost effectiveness to any significant degree.

Because there is no consensus in the cost-effectiveness literature regarding whether and how productivity costs (i.e., indirect costs) should be incorporated into cost-effectiveness analyses (16), this study focused on patient out-of-pocket costs for infertility treatment and did not include indirect costs. However, a comparison of indirect costs between ART and vasectomy reversal would likely benefit vasectomy reversal, given the more intense monitoring and ongoing patient care involved with IVF cycles.

Cost-effectiveness analyses of long-term outcomes must also consider inflation and changing costs and success rates. We chose to exclude these factors in our modeling because of the short time horizon (<3 years) used for the study. Despite these caveats, it is our hope that this study provides important information for physicians, patients, and insurance carriers regarding the various clinical parameters linked with the treatment of vasectomy-associated male infertility.

Markov models, incorporating important variables such as surgeon or ART experience, female partner age, obstructive interval, and cost effectiveness, can guide individual couples' decision making in cases of infertility due to vasectomy. This type of model could be used by both physicians and patients in the clinical decision process. We are currently creating a Web-based tool that permits the use of individual parameters (e.g., costs, reversal results) to determine outcomes for specific situations. Our findings support the opinion that female partner age is particularly critical in determining the most cost-effective treatments for male infertility.

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