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Cost-Effectiveness Analysis Comparing Continuation of ART with Conversion to IUI in Patients with Low Follicle Numbers

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Abstract

Objective—To compare the cost-effectiveness of proceeding with oocyte retrieval versus conversion to intrauterine insemination (IUI) in patients with 4 or fewer mature follicles during assisted reproductive technology (ART) cycles.

Design—Probabilistic decision analysis. The cost-effectiveness of completing ART cycles in poor responders was compared to converting the cycles to IUI.

Setting—Analysis of published data.

Patient(s)—Not applicable.

Interventions—Cost-effectiveness analysis.

Main Outcome Measure(s)—Cost-effectiveness, which was defined as the average direct medical costs per ongoing pregnancy.

Results—In patients with 1 to 3 mature follicles, completing ART was more cost-effective if the cost of a single ART cycle was between \$10,000 – \$25,000. For patients with 4 mature follicles, if an ART cycle cost less than \$18,025, it was more cost effective to continue with oocyte retrieval than to convert to IUI.

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Conclusion(s)—In patients with 4 or fewer mature follicles following ovarian stimulation in ART cycles, it was on average more cost effective to proceed to oocyte retrieval, rather than converting to IUI. However, important factors such as age, prior ART failures, other fertility factors, and medications used in each individual case, need to be considered before this analysis model can be adapted by individual practices.

Keywords

Poor responders; intrauterine insemination; assisted reproductive technologies; cost effectiveness

INTRODUCTION

Many patients undergoing assisted reproductive technology (ART) respond poorly to ovarian stimulation with gonadotropins, for a number of reasons (1-4). Patients with ART cycles resulting in four or fewer follicles over 14 millimeters are often referred to as poor responders (5-7). These ART cycles are usually associated with very low pregnancy rates and high cancellation rates (8). Moreover, a large percentage of poor responders continue to respond poorly in subsequent ART cycles (9). Management options for poor responders include: cancellation, conversion to intrauterine insemination (IUI), or continuation with the ART cycle by proceeding to oocyte retrieval. This is often a difficult decision for both patients and physicians, involving clinical, financial, logistic, and emotional considerations.

The objective of this study was to identify the most cost-effective procedure between conversion to IUI and continuation with oocyte retrieval in patients with four or fewer mature follicles during ART. This study was conducted based on the average outcome data in published literatures and average direct medical costs in clinics across the United States. However, the model utilized in this study may be individualized to assist both patients and physicians in making the decision to proceed with oocyte retrieval or to convert to IUI in patients with 4 or fewer mature follicles.

MATERIAL AND METHODS

Since all probabilities and costs for the decision analysis were obtained from existing publications and publicly available information, this study was exempt from review by the Institutional Review Board.

A decision tree model (Figure 1) was created to compare the societal costs of achieving an ongoing pregnancy between ART cycles that were converted to an IUI vs. ART cycles that continued through oocyte retrieval in patients with one to four mature follicles. For patients with one to four mature follicles, we assumed that ART cycles were either continued or converted to IUI, and that some of the ART cycles that proceeded through oocyte retrievals ended without an embryo for transfer. The cost and probability of each scenario contributed to the final cost analysis. One-way sensitivity analysis was conducted by varying either the ongoing pregnancy rates or individual procedure costs.

A computerized literature search in MEDLINE, EMBASE, and RCT registries covering the period until December 2013 on ART or IUI in poor responders or patients with low follicle

numbers was conducted. No language limitations were applied. The outcome data used in the decision tree model originated from the published peer-reviewed papers identified in this literature review (8, 10-21). The costs were estimated by averaging the charges that were published on 21 fertility center websites located throughout the United States (U.S.) in various geographic regions. These 21 fertility centers were randomly chosen from the largest IVF Clinics in the U.S. with estimated charges available online. The charges included costs for: 1) physician visits, ultrasounds, lab tests and medications for both groups; and 2) oocyte retrieval, embryo transfer, and embryology lab in ART group; or IUI in IUI conversion group. Costs for gonadotropins and hCG were estimated using the listed pricing of Freedom Fertility Pharmacy. We used clinic charges in 2010 US dollars as surrogates for direct costs and then converted to 2013 US dollars by adjusting for inflation using the United States Department of Labor - Bureau of Labor Statistics consumer price index inflation calculator (www.bls.gov/data/inflation_calculator.htm). The ranges used in the sensitivity analyses were based on data from the same public sources. Based on websites from clinics across the US, we estimated the median cost of ART cycles up to and including the hCG trigger was \$9000 in poor responders, ranging from \$5,500 to \$10,500. The median charges for remaining cycles were estimated to be \$5,000 for completion of ART cycles, ranging from \$3,500 to \$10,000; and \$500 for converted IUI cycles, ranging from \$275 to \$700. Therefore, the median cost for the continuation of ART group was \$14,000, which included the cost for ovarian stimulations (\$9000) plus oocyte retrieval and the rest of ART cycle (\$5000); and for the IUI conversion group, the median cost was \$9500, which included the cost for ovarian stimulations (\$9000) plus completion of the cycle with IUI (\$500).

The cost analysis was conducted using the overall average cost to achieve one ongoing pregnancy, which is different from the healthcare cost for an individual patient. Using average pregnancy rates from published studies on poor responders, we calculated the average total cost per ongoing pregnancy for ART patients that were converted to IUI versus ART patients that proceeded with oocyte retrieval, grouped by the number of mature follicles at the time of human chorionic gonadotropin (hCG) trigger. One-way sensitivity analyses were completed for each follicle group to determine the average cost per ongoing pregnancy while maintaining the average pregnancy rates and median procedure costs for completed ART cycles constant, and varying the ongoing pregnancy rates for converted IUI cycles. Sensitivity analyses were also completed to determine whether decreasing ART costs would make IUI conversion more cost-effective by maintaining the average cost per ongoing pregnancy for converted IUI for each follicle group, and varying the cost of a single completed ART cycle across a range of costs for each follicle group from \$10,000 to \$20,000. Similar sensitivity analyses were done varying the cost of converted IUI cycles.

RESULTS

For each patient group, continuation with ART resulted in higher ongoing pregnancy rates on average and lower average total cost per ongoing pregnancy when compared to conversion to IUI (Table 1). For example, patients with 4 mature follicles had an average ongoing pregnancy rate of 12% if the cycles are converted to IUI, compared to 22% if the ART cycles are completed. This resulted in the difference in average cost per ongoing pregnancy, \$79,167 versus \$63,636 respectively (Table 1).

Sensitivity analyses that maintained the average pregnancy rates and costs for completed ART cycles constant, and varied the ongoing pregnancy rates for converted IUI cycles showed that in order for converted IUI cycles to be more cost effective than completion of ART, IUI needs to achieve ongoing pregnancy rates of 3%, 5%, 13.5% and 15%, respectively, in patients with 1, 2, 3 or 4 mature follicles. These rates are much higher than the published average in each follicle group (Table 2).

When maintaining the cost per ongoing pregnancy for converted IUI constant, and varying the cost of a single completed ART cycle, we observed that in the 1 to 3 follicle groups, completing ART was more cost-effective if the cost of a single ART cycle is within the range of \$10,000 to \$25,000. In the 4-follicle group, if an ART cycle costs less than \$18,025, it is more cost effective to proceed with oocyte retrieval than to convert to an IUI. Above \$18,025, converting to IUI was more cost effective (Figure 2a to 2d).

Similar sensitivity analyses were done to determine the effect of varying the cost of converted IUI cycles. In the 1 and 3 follicle group, when we keep the median total cost for ART cycle the same for each follicle group at \$14,000, only when the cost for converted IUI cycle was less than \$5000, would conversion to IUI be more cost effective than continuation with ART. In the 4 mature follicle group, if a converted IUI cycle costs less than \$7,650, it is more cost effective than continuation with ART.

DISCUSSION

At this time, based on the available public data, our decision tree model results suggested that continuation with ART is more cost effective than conversion to IUI in poor responders with four or less mature follicles. Our model was based on published information and involved a probabilistic decision analysis that does not factor in individual patient data such as age, prior poor response, hormonal status nor medications usage. The results of the decision tree model could be adapted by individual practices to help with decision making for poor responders, based on the number of mature follicles and individual patient demographics. Individual practices could use their own pregnancy rates to identify the most cost-effective procedure specific to their own patient population.

The ability to predict pregnancy outcomes after ART is difficult for any patient, and especially difficult for patients with poor response to gonadotropin stimulation. ART is expensive, both financially and emotionally, and the decisions associated with ART become more difficult as follicle counts decrease. There is very little guidance to assist clinicians and patients with making these difficult decisions during ART. The current literature is limited to retrospective cohort studies or case series. In order to best answer the question of which treatment strategy is the best in poor responders, a randomized controlled trial that considers various factors such as age, follicle numbers, infertility history and prior treatments would be ideal. However, enrollment of patients into such a clinical trial could be difficult due to significant financial involvement and considerations in the decision-making process. A cost-effectiveness analysis is a major step toward providing physicians and patients with some guidance when facing these difficult and individualized decisions.

In addition to age, there are biomarkers of ovarian reserve that may be useful in predicting outcomes in patients who are poor responders. Multiple publications have suggested that there is a role for basal FSH in predicting pregnancy outcomes after IVF (3, 22). Since these early studies, there have been investigations of other biomarkers such as antral follicle count (AFC), anti-müllerian hormone (AMH) and inhibin B. Unfortunately, the ability of any of these biomarkers alone to predict pregnancy outcomes has been variable (23). In a more recent study investigators were able to significantly increase the accuracy of predicting ovarian response by combining age, AFC and AMH (24). The ability of the markers to predict pregnancy outcome, however, was poor even when age, FSH, AMH and AFC were considered. The authors concluded that the clinical usefulness of ovarian reserve testing prior to IVF will be limited to the prediction of ovarian response (24, 25).

The difficulty of predicting ovarian response during ART and a lack of large-scale and detailed studies of pregnancy outcomes in poor responders led to several limitations of our study. Individual patients were not evaluated, rather, a cost analysis model was used to predict the financial burdens of conversion to IUI versus oocyte retrieval for patients with 1 – 4 mature follicles. A high percentage of poor responses during ART occur due to age-related decline in fertility. Therefore, age is an important factor in counseling these patients and in making the decision of continuation with the ART cycle versus converting to IUI. However, age was not included as a factor in our decision tree model, due to limited availability of publications that break down pregnancy outcomes in the poor responders based on age groups. The three papers that divided patients into two age groups did not investigate outcomes based on individual follicle numbers (14, 20, 26). One recent study did show that in patients < 40 years of age with 3 or fewer follicles, ART resulted in statistically significantly improved live birth rate compared to IUI conversion. The live birth rates were comparable between the two groups if the patients were older than 40 (21). Because this was the only study that analyzed pregnancy outcomes in poor responders grouped both by age and number of follicles, we did not include age in our decision tree model. However, our sensitivity analyses cover a range of possible pregnancy rates to help overcome this limitation. We were also unable to use live birth rates as the effectiveness measure in the analysis, as the majority of papers on poor responders only include ongoing pregnancy rates and not live birth rates for their clinical outcome measure. Due to the same limitation in available data in existing publications, ovarian stimulation protocols, ovarian reserve status, and multiple pregnancies were not included in the decision tree model. In addition, this study only examined direct medical costs, and did not consider indirect societal costs such as medical leaves or decreased wages during the different treatments.

CONCLUSION

It is often difficult for both patients and clinicians to make the decision on whether to proceed with oocyte retrieval with only 1-4 mature follicles after ovarian stimulation during ART. Our cost-effectiveness analyses using average direct costs showed that it was more cost effective to proceed to oocyte retrieval, rather than converting to IUI. Because this decision tree model was based on published information, it did not factor in individual level data, such as age, prior ART failures, other fertility factors, and medications used in each individual case. However, this model could be adapted by individual practices using their

own patient demographic data and medical costs to help with decision-making in their specific patient populations.

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Figure 1. Decision tree model

○ denotes chance node. ■ denotes decision node.

Figure 2. Sensitivity analysis: varying the cost of ART while maintaining the cost of IUI conversion for the a) 1-follicle group; b) 2-follicle group; c) 3-follicle group; and d) 4-follicle group

The blue diamonds represent the IUI group, and the red squares represent the ART group. In 1- to 3-follicle groups, completing ART was more cost-effective if the cost of a single ART cycle is within the range of \$10,000 to \$25,000. In the 4-follicle group, if an ART cycle costs less than \$18,025, it is more cost effective than conversion to IUI. Above this cost level, converting to IUI was more cost effective.

Table 1

Average ongoing pregnancy rates and total costs per ongoing pregnancy for conversion to IUI vs. continuation with ART in patients with 1 to 4 mature follicles.

Mature Follicle #	Convert to IUI		Continue ART	
	Average Ongoing Pregnancy Rate *	Cost Per Ongoing Pregnancy	Average Ongoing Pregnancy Rate *	Cost Per Ongoing Pregnancy
1	1.6%	\$614,488	4.5%	\$321,977
2	1.7%	\$578,341	7.6%	\$190,644
3	7.0%	\$140,454	20.0%	\$72,445
4	12.0%	\$81,932	22.0%	\$65,859

* The ongoing pregnancy rates were based on estimates from the literature and were used to inform the decision tree model cost estimates.

Table 2

Sensitivity analysis: varying ongoing pregnancy rates of converted IUI cycles. In order for Converted IUI cycles to be more cost effective than completed ART cycles, IUI needs achieve these “threshold” ongoing pregnancy rates.

Mature Follicle #	Ongoing Pregnancy Rate		
	Convert to IUI (Published Average)*	Continue ART (Published Average)*	Threshold rate where IUI becomes more cost effective
1	1.6%	4.5%	3.0%
2	1.7%	7.6%	5.0%
3	7.0%	20.0%	13.5%
4	12.0%	22.0%	15.0%

* The ongoing pregnancy rates for both the IUI and ART groups were based on estimates from the literature and were used to inform the decision tree model cost estimates.