Mild Stimulation versus Conventional IVF: A Cost-Effectiveness Evaluation

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Abstract

Purpose: To compare the strategy for mild stimulation IVF versus conventional stimulation IVF.

Methods: A decision tree analytic model was created to compare IVF with mild stimulation versus convention stimulation in infertile women <38 years of age to evaluate which strategy is the least costly per live birth. Results: Using base-case estimates of costs and probabilities in women <38 years old with unexplained infertility, the cumulative live birth rate in the mild versus conventional stimulation group was 15.8% versus 28.6%, respectively. The average cost for mild and convention IVF was $8789 and $14,364 per arm, respectively. In base case analysis, the ICER was $43,516 representing the additional cost per live birth with conventional IVF. One-way sensitivity analysis evaluated the robustness of the data and revealed a tradeoff in which mild IVF stimulation had lower total costs and also lower live births versus conventional stimulation. Conclusions: Mild stimulation IVF has a lower cost per cycle but is also associated with lower live birth rates. Patient care decisions should be individualized irrespective of cost.

Keywords

Minimal Stimulation, Mild IVF, IVF, Decision Analysis, Cost Analysis

1. Introduction

The introduction of in vitro fertilization (IVF) dramatically improved the ability to help women with unexplained infertility achieve a pregnancy [1] [2]. Minimal or mild stimulation protocols for IVF (mild-IVF) have been developed to achieve a less vigorous ovarian response as compared to conventional stimulations protocols.
(conv-IVF) [3] [4]. Many different approaches of mild stimulation exist, including use of oral agents such as clomiphene citrate or aromatase inhibitors, low-dose exogenous gonadotropins, gonadotropin releasing hormone (GnRH) antagonists, and late follicular phase human chorionic gonadotropin (HCG) injection or lutenizing hormone (LH).

Mild ovarian stimulation has potential advantages over conv-IVF in select patient populations. Due to decreases in follicular number and retrieved oocytes, mild-IVF has been associated with a decrease in the risk of OHSS and multiple pregnancy rates [5]-[10]. Further, the less pronounced hormonal elevations seen with mild-IVF may also be associated with an improvement in endometrial receptivity, potentially less risk of aneuploidy, and an improvement in obstetrical outcomes [11]-[13]. Patient preference is also important, as the psychological demands and the total cost per cycle appear to be less with mild-IVF as compared to conv-IVF [5] [14]-[16].

Mild-IVF may reduce the risk of complications seen with IVF, but an important concern with the use of a mild stimulation protocol is the potential reduction of pregnancy rates [4] [17]. Mild-IVF usually results in a lower total dose of exogenous gonadotropins, fewer clinic visits, fewer oocytes retrieved, and fewer embryos [5] [7]. A decrease in embryo number may lower fresh IVF pregnancy rates, diminish the opportunity for cryopreservation of extra embryos and future frozen embryo transfer (FET), and may lead to reduction in cumulative live birth rate (LBR) [8] [18].

Although European studies have concluded that mild-IVF was cost-effective over conv-IVF when medications were minimized, no such comparison of mild-IVF and conv-IVF has been undertaken in the United States (US) [16] [19] [20]. As both costs and expected pregnancy rates in the United States are, on average, higher than reported European rates, application of a European assessment on cost-effectiveness is difficult in the US [21]-[23]. Therefore, we performed a decision analysis to determine the cost per live birth in women <38 years of age with unexplained infertility who undergo mild-IVF versus those who undergo conv-IVF.

2. Methods and Materials

A decision tree analysis model was developed comparing two strategies, mild-IVF and conv-IVF in infertile women under age 38 years with either unexplained, male or tubal factor infertility in order to determine the cost per live birth. The model was structured using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) as a framework [24]. The model (Figure 1) was designed so that with each cycle, the following possibilities may occur: 1) there will be enough embryos to transfer after fresh mild-IVF without additional embryos for cryopreservation; 2) there will be enough embryos to transfer after fresh conv-IVF with additional embryos for cryopreservation; and 3) there will be enough embryos to transfer after fresh conv-IVF without additional embryos for cryopreservation. If pregnancy does not occur, the conv-IVF model allows for a total of one fresh and one frozen cycle to try to achieve a pregnancy. The base case cohort size was 1000 women. Our local Institutional Review Board does not require approval for decision analysis project.

Figure 1. Simplified decision tree for comparing mild and conventional stimulation for IVF in a cohort of women with unexplained infertility. In this diagram, a square represents a decision node and a circle represent a chance node. In the mild-IVF arm, women go through one fresh cycle. Women in the conv-IVF arm may undergo one fresh and one frozen embryo transfer if embryos were available for cryopreservation.
Our probability inputs for live birth per fresh cycle and cycle cancellation were based on the largest randomized controlled trial comparing conv-IVF and mild-IVF [5]. In this Netherlands-based study by Heijen et al., participants were <38 years of age with unexplained, male or tubal factor infertility. 404 subjects were randomized to either conv-IVF or mild-IVF. The mild-IVF protocol included GnRH antagonist treatment, 150 IU FSH daily starting on cycle day 5, and transfer of a single embryo while the conv-IVF protocol included GnRH agonist treatment, 150 IU FSH daily starting on cycle day 2, and a double embryo transfer [5] [25]. The mean duration of gonadotropin stimulation and number of oocytes retrieved was 8.3 days and 6.9 oocytes (SD 4.8) for mild-IVF and 11.5 days and 8.5 oocytes (SD 4.3) for conv-IVF [5]. The mean total gonadotropin usage was 1307 IU for mild-IVF versus 1832 IU for conv-IVF [5]. Specifically, the LBR per fresh cycle for mild-IVF versus conv-IVF was reported at 15.8% versus 24%, respectively (Table 1). Cycle cancellation rates were 18% for mild-IVF and 8.3% for conv-IVF; however, as input probabilities were based on LBR per cycle, cycle cancellation probabilities were not included as inputs in the model [5].

To estimate base case inputs for supernumery embryo cryopreservation and LBR after frozen embryo transfer, the previously discussed study by Heijen et al. had only a few patients with extra embryos for cryopreservation and a low LBR per FET (1.1%) [5]. As we felt this is not representative of expected success rate after FET, we opted to base LBRs after FET on a large Swedish study by Thurin et al. [26]. In this study, subjects received a conv-IVF stimulation protocol and were randomized to either double fresh embryo transfer or single fresh embryo transfer with a subsequent single-embryo FET. The LBR per FET was 16.4% [26]. Furthermore, we assumed not all patients who underwent conv-IVF would have extra embryos available for cryopreservation. The probability input for cryopreservation of embryos is from a Netherlands based study in which the probability of having excess embryos for cryopreservation after conv-IVF was 37% [16]. In our model, patients pursuing mild-IVF were assumed to not have additional embryos available for cryopreservation or FET. Of note, due to a lack of randomized controlled data from the US on mild-IVF, we based all probability inputs on European studies in order to achieve a cohesive cohort for analysis.

Cost was interpreted from a patient directed medical cost perspective (Table 1). Total costs for a fresh cycle included both medication and procedural costs. We estimated medication costs for both protocols based on an average of costs from known US fertility pharmacies, with an average follicle stimulating hormone (FSH) cost at $0.91 per IU, an average cost for 5 days of GnRH antagonist at $573, and an average cost for a GnRH agonist kit at $149 [27] [28]. We calculated both a total FSH cost and a total stimulation medication costs for mild-IVF and conv-IVF protocols. We estimated procedural IVF costs for conv-IVF (facility, monitoring, procedural and laboratory costs), cryopreservation costs, and FET costs by taking an average of seven different IVF centers in New York, Massachusetts, North Carolina, Texas, Colorado, Illinois, California [29]-[35]. Similarly, for mild-IVF, we took the average of six US clinics that advertise mild-IVF procedural costs (facility, monitoring, procedural and laboratory costs) from New York, North Carolina, Texas, Utah and California [35]-[40]. Total costs for a fresh cycle included both medication and procedural costs. Loss of productivity, obstetrical costs, and indirect costs were not included in this comparison.

The incremental cost-effectiveness ratio (ICER) represents the additional cost per live birth. The ICER was calculated by dividing the cost difference between the two scenarios by live birth difference. A protocol was considered dominated when it was equally or less effective than the alternative but more costly. The robustness of the base-case results was tested using one-way sensitivity analysis by varying probabilities and costs down to one-half and up to two times the baseline estimates (Table 1). In addition, Monte Carlo analysis was performed in which all probability estimates were varied simultaneously and the simulation was run 62,718 cycles (the total number of IVF cycles performed in the US in 2012 in this age group) [23]. The model was built in Microsoft Excel 2013, with the add-in macro Oracle Crystal Ball (version 11.1.2.2) for Monte Carlo simulation.

3. Results

In our analytic model for women <38 years old with unexplained infertility, the cumulative LBR with mild-IVF versus conv-IVF was 15.8% and 28.6%, respectively (Table 2). The average cost per woman was $8789 and $14,364 for the mild-IVF and the conv-IVF arms, respectively. Thus, the mild-IVF arm had a lower percentage of live births and lower total costs. As the conv-IVF arm had a 12.8% higher LBR than mild-IVF, the ICER was $43,516, representing the additional cost per live birth with conv-IVF.

Using one-way sensitivity analysis for each input variable, the model was sensitive to changes in LBR after IVF (Table 3). When varying the effectiveness (LBR) of mild-IVF and conv-IVF, in most scenarios there is a
### Table 1. Probability and cost variables.

<table>
<thead>
<tr>
<th>Probability variables</th>
<th>Base case</th>
<th>Ranges</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild-IVF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle cancelation</td>
<td>0.180</td>
<td>0.090 - 0.360</td>
<td>[5]</td>
</tr>
<tr>
<td>Live birth per cycle</td>
<td>0.158</td>
<td>0.079 - 0.316</td>
<td>[5]</td>
</tr>
<tr>
<td><strong>Conv-IVF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cycle cancelation</td>
<td>0.083</td>
<td>0.042 - 0.166</td>
<td>[5]</td>
</tr>
<tr>
<td>Live birth per cycle</td>
<td>0.240</td>
<td>0.120 - 0.480</td>
<td>[5]</td>
</tr>
<tr>
<td>Cryopreserved embryos</td>
<td>0.370</td>
<td>0.185 - 0.740</td>
<td>[15]</td>
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<tr>
<td>Live birth after FET</td>
<td>0.164</td>
<td>0.082 - 0.328</td>
<td>[25]</td>
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</table>

<table>
<thead>
<tr>
<th>Cost variables</th>
<th></th>
<th></th>
<th></th>
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<tbody>
<tr>
<td><strong>Mild-IVF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FSH cost</td>
<td>1189</td>
<td>595 - 2378</td>
<td>[5] [26] [27]</td>
</tr>
<tr>
<td>Total medication cost</td>
<td>2399</td>
<td>1200 - 4798</td>
<td>[5] [26] [27]</td>
</tr>
<tr>
<td>Fresh transfer cycle</td>
<td>8789</td>
<td>4395 - 17,578</td>
<td>[5] [26] [27] [34] - [39]</td>
</tr>
<tr>
<td><strong>Conv-IVF</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total FSH cost</td>
<td>1667</td>
<td>834 - 3334</td>
<td>[5] [26] [27]</td>
</tr>
<tr>
<td>Total medication cost</td>
<td>2601</td>
<td>1301 - 5202</td>
<td>[5] [26] [27]</td>
</tr>
<tr>
<td>Fresh transfer cycle</td>
<td>12,991</td>
<td>6496 - 25,982</td>
<td>[5] [26] - [34]</td>
</tr>
<tr>
<td>Cryopreservation and storage</td>
<td>1150</td>
<td>575 - 2300</td>
<td>[28] - [34]</td>
</tr>
<tr>
<td>FET cycle</td>
<td>3370</td>
<td>1685 - 6740</td>
<td>[28] - [34]</td>
</tr>
</tbody>
</table>

1All cost variables reported in 2015 USD; 2Calculated from average cost per IU FSH; 3Total cost of GnRH agonist or GnRH antagonist, FSH, HCG and progesterone; 4Total cost including all medications, facility, and lab costs.

### Table 2. Base case analysis results.

<table>
<thead>
<tr>
<th></th>
<th>Cost</th>
<th>Incremental cost</th>
<th>Effectiveness</th>
<th>Incremental effectiveness</th>
<th>ICER</th>
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<tr>
<td><strong>Mild-IVF</strong></td>
<td>8789</td>
<td></td>
<td>15.8</td>
<td></td>
<td></td>
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<tr>
<td><strong>Conv-IVF</strong></td>
<td>14,364</td>
<td>5575</td>
<td>28.6</td>
<td>12.8</td>
<td>43,516</td>
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</table>

Note: based on a simulated cohort of 1000 women; 1Cost reported as average cost per woman in 2015 USD; 2Effectiveness reported as % live births; 3ICER = Incremental cost-effectiveness ratio.

### Table 3. One-way sensitivity analysis results.

<table>
<thead>
<tr>
<th></th>
<th>Value</th>
<th>Incremental cost</th>
<th>Incremental effectiveness</th>
<th>ICER</th>
<th>Interpretation</th>
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</thead>
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<tr>
<td><strong>Effectiveness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mild-IVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.07 (5575)</td>
<td>(20.7)</td>
<td>26,918</td>
<td>tradeoff</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.32 (5575)</td>
<td>3.0</td>
<td>(186,564)</td>
<td>mild-IVF</td>
<td></td>
</tr>
<tr>
<td><strong>Conv-IVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0.12 (5276)</td>
<td>(1.5)</td>
<td>371,777</td>
<td>tradeoff</td>
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<tr>
<td>High</td>
<td>0.48 (1347)</td>
<td>(35.4)</td>
<td>14,922</td>
<td>tradeoff</td>
<td></td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mild-IVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4395 (9969)</td>
<td>(12.8)</td>
<td>77,813</td>
<td>tradeoff</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>17,578 3214</td>
<td>(12.8)</td>
<td>conv-IVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Conv-IVF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>6496 1902</td>
<td>(12.8)</td>
<td>conv-IVF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>25,982 (9709)</td>
<td>(12.8)</td>
<td>75,781</td>
<td>tradeoff</td>
<td></td>
</tr>
</tbody>
</table>

Note: based on a simulated cohort of 1000 women. 1Cost reported as average cost per woman in 2015 USD, negative values in parenthesis; 2Effectiveness reported as % live births, negative values in parenthesis; 3ICER = Incremental cost-effectiveness ratio; 4Interpretation reported as tradeoff (mild-IVF with lower costs but lower effectiveness), mild-IVF (mild-IVF is cost-effective), or conv-IVF (mild-IVF is not cost-effective).
tradeoff with mild-IVF—costs are lower but LBRs are lower as well. In the scenario where mild-IVF is at maximum hypothetical effectiveness (32% LBR), mild-IVF is cost-effective over conv-IVF. When varying the costs for mild-IVF and conv-IVF, conv-IVF dominated mild-IVF when either mild-IVF is at maximum cost or conv-IVF is at minimum cost. In the other scenarios, mild-IVF was again a tradeoff with lower costs and lower LBRs.

Using Monte Carlo simulation with 62,718 cycles over 1000 trials, mild-IVF resulted in a median of 9623 fewer live births and the median ICER was $37,956 additional cost per live birth with conv-IVF. In the simulation, mild-IVF had lower costs and fewer live births in over 90% of scenarios.

4. Discussion

Our study is the first to use an analytic decision model to compare the cost per live birth using US cost-estimates for mild-IVF and conv-IVF. Our base-case and most sensitivity analyses resulted in a tradeoff in which mild-IVF has a lower cost and a lower effectiveness than conv-IVF. The one scenario which found mild-IVF to be cost effective required mild-IVF to be at maximum hypothetical effectiveness (32%). This should be cautiously interpreted and is a highly unlikely scenario, as mild-IVF would need to be more have higher LBRs than conv-IVF (32% versus 24%, respectively) in order to be cost effective. Further, the two scenarios where conv-IVF dominated mild-IVF are also unlikely, requiring mild-IVF to have a greater total cost than conv-IVF. The Monte Carlo simulation further confirmed the tradeoff with mild-IVF resulting in lower costs but lower effectiveness in the vast majority of scenarios.

Previous cost-effectiveness evaluations comparing mild-IVF and conv-IVF have been limited to only a European perspective. Polinder et al. evaluated subjects randomized to either mild-IVF or conv-IVF with the outcome of cumulative 1 year LBRs after multiple cycles [20]. In this analysis, patients who underwent mild-IVF had an increase in total number of cycles completed throughout the year, and mild-IVF was determined to be a cost-effective alternative to conv-IVF [20]. A main contributing factor to the lower cost for mild-IVF was the inclusion of obstetrical and neonatal costs associated with multiple gestations in the conv-IVF group [20]. Further, Groen et al. performed a cost-effectiveness evaluation after retrospective review of patients who received mild-IVF or conv-IVF [16]. Depending on the number of cycles per patient, mild-IVF was at times cost-effective when medications were minimized [16]. However, as patients were not randomized in this study, selection bias may exist in which subjects were allocated a treatment option in a preferential fashion, thus skewing the results [16]. Due to these limitations, and as there are substantial differences in costs between Europe and the US, it is difficult to apply these results to clinical practice in the US.

As with all decision analytic models, the strength of our conclusion is dependent upon the validity of our data inputs. In our model, the base case inputs for live birth per fresh cycle, excess embryos for cryopreservation, and frozen embryo transfer live birth rates are all based on European studies in the same era in order to achieve a cohesive cohort for analysis. We used the largest published randomized control trial as the base for LBRs after fresh mild-IVF and conv-IVF cycles [5]. As this study is randomized, variability and provider initiated selection bias between treatment group assignment was minimized, thus improving validity. Further, LBRs in this study (15.8% for mild-IVF) are consistent with the LBR for mild-IVF reported in another randomized European study by Hohmann et al. (16%), supporting the validity of these results [5] [41]. However, LBRs in these European studies are lower than expected US rates [5] [16] [23] [26]. If our model compared the LBR from Heijen et al. for mild-IVF with US data for live birth per cycle in women <38 years, conv-IVF would dominate the model due to markedly higher US LBRs [5] [23] [42]. Therefore, because IVF practices and success rates differ between Europe and the US, we felt that the strongest model included LBRs for mild-IVF, conv-IVF, and FET based on European studies, as this would give us the most direct comparison. Our sensitivity analysis allowed for further broad analysis of the varying LBRs to better include scenarios that may approximate US outcomes.

Our model focused solely on live birth, we did not include differences in the potential for multiple gestation, potential losses in productivity, or the emotional burden associated with infertility treatment. Multiple gestation has a significant impact on obstetrical and neonatal costs, and inclusion of this factor in our model would significantly increase the cost of conv-IVF [43]-[45]. However, with the gaining acceptance of elective single embryo transfer in the US, the transfer of a single embryo, regardless of stimulation protocol, is likely the most direct way to decrease the risk of multiple gestation [46]-[48].

Unfortunately, there is not published US data on the cost for mild-IVF. European studies that report a break-
down for the cost of mild-IVF and conv-IVF have very similar monitoring and procedural costs [5] [16] [20]. However, many US infertility practices advertise decreased costs for “mild”, “mini”, or “minimal” IVF as compared to conv-IVF. In our model, we opted to use an average of advertised costs in order to most closely reflect the difference in monitoring charges with a mild versus conventional stimulation approach. Regional bias was minimized by averaging IVF rates for both mild-IVF and conv-IVF from clinics across the US and sensitivity analysis allowed for further broad analysis of the costs. The total costs in our model for conv-IVF (procedural and medication costs) and FET were similar to previously reported US rates [21] [43] [49]-[51].

The difference in conv-IVF stimulation protocols between European studies and conventional US practice may impact interpretation of our model. In the reported base-case study, the FSH dose in conv-IVF was limited to 150 IU per day (average 1832 IU per cycle) [5] [41]. This is lower than what is reported in US studies, and may have an impact on the degree of stimulation, number of oocytes retrieved, and total costs. A surveillance report in the US revealed a mean FSH dose per GnRH agonist cycle of 2186 IU [52]. Although this is higher than the mean FSH dose in our conv-IVF group, the overall FSH cost difference is limited ($322 USD) [5] [52]. Thus, we would not expect an increase in FSH dose in conventional US protocols to make a substantial difference in the results of our model. Interestingly, the overall medication cost in our model was not markedly different for the mild-IVF and conv-IVF groups. This is likely due to the balance between the cost difference in total FSH dose per protocol and the price difference between GnRH agonist and antagonist treatment. Although the total length of stimulation and total FSH dose is less in mild-IVF, GnRH antagonist is more expensive than agonist treatment [5] [27] [28] [53]. It is important to note that our results apply to the mild-IVF protocol used in our model, which includes GnRH antagonist treatment and exogenous gonadotropins. Other ovarian stimulation protocols that avoid the use gonadotropins (such as natural cycle or oral agents for ovarian stimulation), would be expected to result in a decreased cost and lower LBRs and are not included in the scope of the analysis.

5. Conclusion
Mild stimulation protocols have lower costs and also lower LBRs when compared with conventional stimulation. Although mild stimulation may be advantageous for select patients, mild-IVF should not be promoted over conv-IVF on the basis of cost-saving without disclosing a decrease in LBRs. Decisions regarding the appropriate stimulation plan should be individualized for the patient based on clinical reasoning and patient preferences. Additional randomized control trials in the US comparing mild-IVF and conv-IVF may help clarify the potential benefits of a mild stimulation protocol.

Conflict of Interest
The authors declare that they have no conflict of interest.

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