Cost-effectiveness in reproductive medicine
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Citation for published version (APA):

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Cost-effectiveness of Treatment Strategies in Women with PCOS and CC Failure

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Fulco van der Veen
Ben Willem J. Mol

Submitted
Abstract

The aim of this study was to evaluate the cost-effectiveness of scenarios for women with PCOS who ovulate on Clomiphene Citrate (CC), but did not conceive after 6 cycles. A decision-analytic-framework was developed for a 30 year old women. We evaluated six treatment scenarios: [1] Three cycles of IVF [2] Continuation of CC with six cycles, followed by three cycles of IVF in case of no birth [3] Six cycles of Gonadotrophins and three cycles of IVF [4] Twelve cycles of Gonadotrophins and three cycles of IVF [5] Continuation of CC with six cycles, six cycles of Gonadotrophins and three cycles of IVF [6] Continuation of CC with six cycles, twelve cycles of Gonadotrophins and three cycles of IVF. Two year cumulative birth rates were 58%, 74%, 89%, 97%, 93% and 98% and costs per couple were €9,518, €7,530, €9,711, €9,764, €7,651 and €7,684 for scenario 1, 2, 3, 4, 5 and 6 respectively. Scenario 2 was the lowest cost option. The extra cost per at least one live birth for scenario 5 was €629 and for scenario 6 €630. In women with PCOS and CC failure after 6 cycles, continuation of treatment with 6 cycles of CC followed by 6-12 cycles of Gonadotrophins and IVF is potentially cost-effective. These results should be confirmed in a randomized clinical trial.
Cost-effectiveness of Treatment in Women with PCOS

**Introduction**

Anovulation is one of the leading causes of female infertility. About 80% of anovulatory women have a WHO type II or normogonadotropic normoestrogenic anovulation, and polycystic ovary syndrome (PCOS) is the most common form of WHO II anovulatory infertility.

Clomiphene citrate (CC) is widely used as a first line ovulation induction agent (Kousta et al., 1997). Systematic reviews and meta-analyses have shown that CC is indeed the best primary treatment option in therapy-naïve women with PCOS (Brown et al., 2009; Moll et al., 2008). Although 60% to 85% of women starting ovulation induction with CC will ovulate, only about 50% of these couples will have conceived after 6 cycles (Neveu et al., 2007).

When anovulatory women ovulate after CC, but fail to conceive after 6 cycles, subsequent treatment scenarios are diverse in current practice. Treatment may continue with CC for another 6 cycles or may switch to ovulation induction with gonadotrophins.

The ESHRE/ASRM consensus guideline recommends that therapy naïve women should start with six cycles of CC, but continuation until 12 cycles could be considered (ESHRE/ASRM, 2008). This guideline also recommends that second line treatment with gonadotrophins should not exceed six ovulatory cycles, but evidence underpinning this is not provided. Costs are considered but no definite recommendation is given concerning cost-effectiveness (ESHRE/ASRM, 2008).

From a cost effectiveness point of view, it is thus unclear whether and how long one should continue with CC, or whether one should switch to ovulation induction with gonadotrophins or even IVF in women with PCOS that ovulate on CC, but failed to conceive after 6 cycles. Therefore we evaluated the cost-effectiveness of different treatment scenarios in these women.

**Materials and methods**

A Markov decision tree was constructed for women with PCOS who ovulate on CC but failed to conceive after 6 ovulatory cycles. The crucial choice was whether to stick to CC or to switch to gonadotrophins, and when to proceed to IVF. To balance the choices for treatment, we defined six scenarios (Figure 1).

Scenario 1 represented a scenario in which women received a maximum of three cycles of IVF. Scenario 2 consisted of an additional six cycles of CC and a maximum of 3 cycles of IVF in case no live birth was achieved. In scenario 3 six cycles of gonadotrophins were followed by a maximum of three cycles of IVF. Scenario 4 started with 12 cycles of Gonadotrophins and in case of no live birth a maximum of three cycles of IVF was given. Scenario 5 consisted of an additional 6 cycles of CC, six cycles of gonadotrophins and three cycles of IVF. In scenario 6, 6 additional cycles of CC were followed by 12 cycles of gonadotrophins and a maximum of three cycles of IVF in case of no live birth.

For all six scenarios, the treatment costs and pregnancy probabilities were calculated over a two year period. Cycle length was set at one month. We used a time frame of two years, because in this period we could test all scenarios. Due to this short time frame, no discounting was applied. We did not include drop-out rate in our main analysis, since
we wanted to show the maximum possible gain, but we tested the effect of drop-out in sensitivity analysis. We did not include the risk of OHSS, as chronic low-dose step up FSH regimens virtually is eliminates OHSS (Homburg, 2005).

The outcome was defined as live birth of at least one child. Estimates for the base-case scenario and ranges for sensitivity analyses are summarized in table 1 and were derived from peer reviewed literature, as referenced.

The cost calculation was made according to the Dutch situation in the year 2010; hence costs were adjusted according to the consumer price index (CBS, Statistics Netherlands, 2010). We assumed that in this period no significant cost changes in the treatment protocol occurred except for inflation. The model was built from a health care perspective.

**Details of computer simulation model**

*Patient characteristics*

Our base-case calculation was centred on a woman with PCOS who failed to conceive after 6 ovulatory cycles with CC. As the average female age is 30 years in most studies on PCOS, we used this age as our reference point (Brown et al., 2009).
Table 1. Base-case assumptions and used distributions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base case assumption</th>
<th>Distribution</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Live birth probabilities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene Citrate</td>
<td>Cycle 1-6</td>
<td>0.075</td>
<td>Normal (0.04 - 0.11)*</td>
</tr>
<tr>
<td>Gonadotrophins</td>
<td>Per cycle</td>
<td>0.196</td>
<td>Normal (0.98 - 0.29)*</td>
</tr>
<tr>
<td>IVF female age 30-31</td>
<td>Cycle 1</td>
<td>0.277</td>
<td>Normal (0.14 - 0.42)*</td>
</tr>
<tr>
<td></td>
<td>Cycle 2</td>
<td>0.253</td>
<td>Normal (0.13 - 0.38)*</td>
</tr>
<tr>
<td></td>
<td>Cycle 3</td>
<td>0.219</td>
<td>Normal (0.11 - 0.33)*</td>
</tr>
<tr>
<td>IVF female age 32</td>
<td>Cycle 1</td>
<td>0.273</td>
<td>Normal (0.14 - 0.41)*</td>
</tr>
<tr>
<td></td>
<td>Cycle 2</td>
<td>0.249</td>
<td>Normal (0.12 - 0.37)*</td>
</tr>
<tr>
<td></td>
<td>Cycle 3</td>
<td>0.215</td>
<td>Normal (0.11 - 0.32)*</td>
</tr>
<tr>
<td><strong>Probability of twins per treatment</strong></td>
<td>Probability/cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene Citrate</td>
<td>0.1</td>
<td>Normal (0.08 - 0.13)</td>
<td>Eijkemans et al.; Kousta et al.; Schenker et al.; Scialli</td>
</tr>
<tr>
<td>Gonadotrophins</td>
<td>0.25</td>
<td>Normal (0.15 - 0.40)</td>
<td>Jacobs and Agrawal; Lenton</td>
</tr>
<tr>
<td>IVF</td>
<td>0.11</td>
<td>Normal (0.05 - 0.16)*</td>
<td>NVOG</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clomiphene Citrate</td>
<td>500 (250-750) mg</td>
<td>€ 0.01</td>
<td>€ 5</td>
</tr>
<tr>
<td>Gonadotrophins</td>
<td>814 (333-1785) IE</td>
<td>€ 0.41</td>
<td>€ 334</td>
</tr>
<tr>
<td>IVF</td>
<td>3,12</td>
<td>€ 0.41</td>
<td>€ 334</td>
</tr>
<tr>
<td>Cycle monitoring</td>
<td>410</td>
<td>€ 0.41</td>
<td>€ 334</td>
</tr>
<tr>
<td>Singleton pregnancy</td>
<td>2,89</td>
<td>€ 0.41</td>
<td>€ 334</td>
</tr>
<tr>
<td>Twin pregnancy</td>
<td>15,28</td>
<td>€ 0.41</td>
<td>€ 334</td>
</tr>
</tbody>
</table>

* Range based on expert opinion

** Index year 2010
Live birth probabilities

Estimates of live birth probabilities per cycle for CC were based on a recent Cochrane review (Brown et al., 2009). The average probability of live birth was 12.2%. As several studies have shown that the highest live birth rate is seen in the first two ovulatory cycles with CC, we assumed that live birth rate was 20% in the first two cycles and decreased to 7.5% per cycle in subsequent cycles 3 to 6, reflecting an average of 12.2% per cycle. If a live birth was not achieved in the first 6 cycles, live birth probabilities decline, but it is no known with what rate per cycle (Kousta et al., 1997; Hammond et al., 1983). Therefore in our analysis we assumed a steady live birth rate of 7.5% per ovulatory cycle with CC after 6 months.

The live birth probabilities per cycle for gonadotrophins were also based on a recent review, that showed an average probability of live birth of 19.6% for gonadotrophins (Nahuis et al., 2010).

We derived live birth probabilities for IVF from a prospective cohort study performed between 2002 and 2004 (Lintsen et al., 2007). Since we assumed our population to be 30 years at the beginning of the model, we considered IVF live birth rates in the range of those of 30 to 32 year old women. In our analysis we included up to three IVF cycles because this is common practice in Europe (Anderson et al., 2007). In our model we assumed that natural conception did not occur.

Twin probability

The probability of conceiving a twin was included in the model, since probabilities differ across treatments. The probability of conceiving a twin with CC was set at 10%, with gonadotrophins at 25% and with IVF at 11% (Kousta et al., 1997; ESHRE/ASRM, 2008; Bayram et al., 2004; Eijkemans et al., 2003; Guzick et al., 2007; Nederlandse vereniging van Obstetrie en Gynaecologie (NVOG), 2009; Schenker et al., 1981; Scialli, 1986).

Costs

Our analysis was performed from a healthcare perspective; therefore only direct medical costs were included. We included the costs of CC per cycle, gonadotrophins per cycle, cycle monitoring, IVF per cycle, the costs of a singleton and twin pregnancy until 6 weeks post-partum.

Unit costs of CC and gonadotrophins were derived from the Dutch healthcare insurance board (CVZ) (Health insurance board, 2009). Costs per cycle were calculated according to average dosages in the used reviews (Brown et al., 2009; Nahuis et al., 2010). Costs per IVF cycle were derived from the Dutch Umbrella study on fertility treatments (Merkus, 2006). The cost of a singleton and twin pregnancy until 6 weeks post-partum were derived from a cost-analysis in the Netherlands (Lukassen et al., 2004).

All monetary units were converted into the equivalent of 2010 using the consumer price index (CBS, Statistics Netherlands, 2010). We assumed that in this period no significant cost changes in the treatment protocol occurred except for inflation. The costs were €5 for a CC cycle, €334 for a gonadotrophin cycle, €410 for cycle monitoring, €3119 for an IVF cycle and €2,891 for a singleton pregnancy and €15,276 for a twin pregnancy (Table 1).
Outcomes
Cumulative live birth rates of at least one child were determined for each scenario, as were the estimated costs. Using these values, we computed the costs per live birth and the incremental cost-effectiveness ratio (ICER). The lowest cost option was used as a reference scenario since a no treatment scenario at this stage of the treatment is not realistic. The incremental cost-effectiveness ratio represents the extra costs per live birth between two scenarios. These costs are calculated by dividing the differences in costs by the difference in live birth rate of two scenarios.

Sensitivity analysis
To address the uncertainty regarding our assumptions we carried out one-way and probabilistic sensitivity analyses. In our base case calculation no discounting was applied, in one-way and multi-way sensitivity analysis we tested the effect of different discounting rates for costs and effects.

In one-way sensitivity analysis we varied all variables independently. Thresholds of all used variables were determined. We determined if and when a variable changed our main conclusions. The threshold value represents the value of a variable above or below which another scenario is preferred. Since we assumed in our model that no spontaneous live birth could occur, we tested the in sensitivity analysis what the effect would be if spontaneous live birth did occur. We also tested the effect drop-out rate as a continuous rate in all cycles.

In probabilistic sensitivity analysis the uncertainty in each parameter is quantified in terms of a probability distribution of this parameter. For this analysis, distributions were fitted for all parameters in the model. We were not able to set beta distributions, hence normal distributions were fitted. The normal distributions were calculated according to the confidence interval from the study or by the plausible range provided by expert opinion (Briggs et al., 2006). For the probabilistic sensitivity analysis, 5,000 iterations of 5,000 women were performed. To visualize the probability of the optimal scenario based on the willingness to pay, cost-effectiveness acceptability curves were computed. The willingness to pay expresses society’s willingness to pay for a live birth. The ranges and values of all variables used in the sensitivity analyses are shown in table 1.

To address the effect of time to pregnancy resulting in live birth, a threshold analysis was performed, in which a live birth was discounted per month and per year. The effect of discounting is, for example, that a live birth achieved now is valued more than a live birth achieved one year from now.

We performed our analysis by using a computer-generated Markov model (TreeAge Pro 2009, Tree Age Inc, Williamstown, MA, USA). We did not need IRB approval for this research.

Results
Cumulative live birth after two years was 58% for scenario 1, 74% for scenario 2, 89% for scenario 3, 97% for scenario 4, 93% for scenario 5 and 98% for scenario 6. Costs per couple were €9,518, €7,530, €9,711, €9,764, €7,651 and €7,684, respectively. (figure 2)
Chapter 6

The lowest cost option was scenario 2. The extra cost per at least one live birth (ICER) for scenario 5 was €629 and for scenario 6 €630 compared to scenario 5. These two scenarios dominated the other three scenarios. (figure 2)

Sensitivity analyses
One-way sensitivity analysis showed that if live birth probabilities of gonadotrophins would increase above 21% per cycle or if the probability of conceiving a twin after gonadotrophins would decrease below 22.8%, scenario 6 would be the dominant scenario. Also if the probability of conceiving a twin with IVF would increase above 15%, scenario 6 would become dominant.

If the drop-out rate per cycle CC, FSH and IVF was more than 1%, scenario 2 became the lowest cost option. Scenario 4 became the next best option, with an ICER of €123,959, compared to scenario 2.

If the cost of cycle monitoring would decrease below €357 or the cost of a twin pregnancy would decrease below < €13,840, scenario 6 would become the dominant scenario. The remaining variables were robust, i.e. no threshold could be found within the plausible ranges.

Time to pregnancy resulting in live birth
The impact of time to live birth was addressed by discounting a live birth per month and per year. If live birth was discounted, our conclusions based on the extra cost per live birth did not change. We did find a threshold for costs per live birth; if live birth was discounted with more than 11% per month, scenario 3 and 4 would become cheaper than scenario 5 and 6.

Probabilistic sensitivity analysis
The results of the probabilistic sensitivity analysis remained stable for our model and did not alter our baseline results. (table 2) The cost-effectiveness acceptability frontier showed that if the willingness to pay (expressing society’s willingness to pay for a live

![Incremental cost-effectiveness plane](image)

*The lowest cost option (scenario 2) is used as a reference. Incremental cost and effects of the other scenario’s are calculated compared to the reference.*

**Figure 2.** Incremental cost-effectiveness plane
birth) was assumed to be less than €800, scenario 2 had the highest probability to be the most cost-effective scenario. If the willingness to pay would rise above €800 per extra live birth, scenario 6 had the highest probability to be cost-effective.

**Discussion**

In this study we evaluated the cost and effects of different treatment scenarios for women with PCOS who did not conceive after 6 ovulatory cycles with CC. Our study showed that, after an initial failed number of 6 cycles, a continuation with CC for 6 cycles followed by 3 cycles of IVF (scenario 2) was the least expensive strategy. Continuation of CC with 6 cycles, followed by 6 to 12 cycles of gonadotrophins and 3 cycles of IVF in case of no live birth (scenario 5 and 6), was more expensive but also generated a higher live birth rate, i.e. 93% versus 98%. Whether this scenario is considered to be cost-effective depends on the willingness to pay per extra live birth.

It is counterintuitive that a long treatment protocol is more cost-effective than a short protocol. This is due to the low costs of CC; as more women conceive during treatment with CC, less women will proceed to the more expensive treatments with Gonadotrophins and the even more expensive IVF. However, not only costs, but also time to pregnancy resulting in live birth is an important factor. We discounted live birth to test the effect of time to pregnancy. Since discounting did not effect our conclusions, the issue of time to pregnancy had no influence from a cost-effectiveness point of view.

Most studies concerning pregnancy or live birth rates rates in women who failed to conceive after CC focussed on rates per cycle or on the first few cycles. No data of long term treatment-scenarios are available, which are necessary for patients, clinicians, health economists and

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**Table 2. Outcome of the probabilistic sensitivity analysis**

<table>
<thead>
<tr>
<th>Scenario*</th>
<th>Live Birth (%) Mean (95% CI)</th>
<th>Cost per couple (€) Mean (95% CI)</th>
<th>ICER (€) Mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1 (3 cycles IVF)</td>
<td>0.567 (0.320-0.763)</td>
<td>€ 9,487 (€ 6,897 - € 12,144)</td>
<td>dominated</td>
</tr>
<tr>
<td>Scenario 2 (6 cycles CC, 3 cycles IVF)</td>
<td>0.726 (0.549-0.856)</td>
<td>€ 7,548 (€ 5,765 - € 9,627)</td>
<td>Reference</td>
</tr>
<tr>
<td>Scenario 3 (6 cycles FSH, 3 cycles IVF)</td>
<td>0.883 (0.810-0.938)</td>
<td>€ 9,706 (€ 8,130 - € 11,399)</td>
<td>dominated</td>
</tr>
<tr>
<td>Scenario 4 (12 cycles FSH, 3 cycles IVF)</td>
<td>0.968 (0.945-0.984)</td>
<td>€ 9,769 (€ 7,983 - € 11,666)</td>
<td>dominated</td>
</tr>
<tr>
<td>Scenario 5 (6 cycles CC, 6 cycles FSH, 3 cycles IVF)</td>
<td>0.926 (0.873-0.962)</td>
<td>€ 7,688 (€ 6,342 - € 9,250)</td>
<td>€ 796 (-€ 7,082 - € 9,203)</td>
</tr>
<tr>
<td>Scenario 6 (6 cycles CC, 12 cycles FSH, 3 cycles IVF)</td>
<td>0.980 (0.963-0.991)</td>
<td>€ 7,728 (€ 6,309 - € 9,407)</td>
<td>€ 797 (-€ 7,083 - € 9,315)</td>
</tr>
</tbody>
</table>

*All options referenced to the low cost option
policy makers if they are to make an informed choice about treatment strategies for PCOS, since treatment may involve many cycles over a long period of time. It is therefore essential to quantify the assumptions used in this model in a randomized controlled trial.

This trend on only reporting the first or the first few cycles is also found in the data of CC. There is little known about the live birth rates in consecutive cycles of CC. Two studies showed that live birth rates decline in subsequent cycles, but it is unclear with what rate, especially after 6 cycles (Kousta et al., 1997; Hammond et al., 1983). Therefore, we assumed a constant rate after of live birth in the CC cycles, which we tested in sensitivity analyses. Irrespective of the probability of live birth after a CC cycle our conclusions remained the same.

Also the effectiveness of gonadotrophins in repeated cycles is uncertain, as most gonadotrophins studies only report on the first few cycles (Nahuis et al., 2010). If mean live birth probabilities per gonadotrophins cycle would increase above 21%, a scenario with 6 cycles of CC, 12 cycles of gonadotrophins, followed by 3 cycles of IVF, would become the dominant scenario. If live birth per cycle declined, our conclusions remained the same.

In our analyses we did not include intra-uterine insemination (IUI) because there is no evidence in favor of IUI versus coitus in women with PCOS that did not conceive after 6 ovulatory cycles with CC. As IUI requires more hospital visits and is more expensive and burdensome for couples, applying IUI should only be considered if it results in significantly more pregnancies (ESHRE/ASRM, 2008; Dickey et al., 1993; Kolibianakis et al., 2004; Randall & Tempelton, 1991).

Another issue that we need to address is that the guidelines in economic research recommend to use the most cost-effective alternative intervention currently available as a comparator (Drummond & Jefferson, 1996). Since in ovulation induction, the guidelines do not agree on the most cost-effective intervention, we decided to use the lowest cost option as a comparator. Also our main outcome was the birth of at least one child. In our analysis we did include the costs for a singleton or twin pregnancy but we did not ‘count’ twin pregnancy to result in two children, because this would favor scenarios in which twins occur.

Our study is a long term cost-effectiveness study, comparing different treatment scenarios for women with PCOS who did not conceive after 6 ovulatory cycles. There is one other study reporting on long term treatment scenarios for women with PCOS (Eijkemans et al., 2005). This study compared a standard scenario of CC, followed by FSH and IVF to a scenario at which the choice between CC, FSH or IVF was dependable on age, body mass index, androgen levels and cycle duration.

This analysis was based on overall live birth rates and not as ours on cycle level and therefore difficult to compare to our study. This study found that CC followed by FSH and IVF was an efficient treatment protocol for women under 30 and for women above 30, gonadotrophins could be omitted.

Since the costs of CC are so low, one could also assume that continuation of CC with more than 12 cycles could be even more cost-effective. Since there is a consensus that it is best to limit a patient’s exposure to CC to 12 treatment cycles, as additional cycles may place the woman at increased risk of borderline ovarian tumours, we had a maximum of 12 cycles in our model (Rossing et al., 1994).
Our analysis showed that in women who fail on CC, the continuation with 6 cycles of CC, followed by 6 or 12 cycles with gonadotrophins, followed by IVF were the most-cost-effective scenarios. We found in our sensitivity analysis that if IVF cycle costs would increase to €3,240, if cycle monitoring cost would decrease to €357, if gonadotrophins cost would decrease below €281, or if the cost of a twin pregnancy would decrease below €13,840, 6 cycles of CC, with 12 cycles of gonadotrophins followed by IVF, would become the dominant scenario (scenario 6). Also if the probability of twins after gonadotrophins would decrease below 22.8%, or if the probability of twins after IVF would increase to 15%, scenario 6 would become the dominant scenario.

At present, it might be difficult to convince women to continue CC again for another 6 months, to switch to 12 months of gonadotropins thereafter due to lack of data. Consequently, according to current standards, our scenario might be unrealistic from a clinical perspective. It is our unreserved feeling that the purpose of science is to challenge existing practice with hypotheses and data. Our article addresses the cost-effectiveness of continuing treatment of women with Clomiphene Citrate (CC) after 6 cycles and shows that this strategy could potentially be very cost effective, which is important data in this era of health budget restraints. As fertility care specialist we are obliged to take costs and effects into considerations and promote the best balance between the two. This is what doctors in the twenty first century should be doing and in itself also supports the notion of patient centeredness and shared decision making. Therefore we conclude that in women who failed to conceive after 6 cycles of CC the most cost effective treatment scenario seems to be a continuation of 6 cycles of CC, followed by 6-12 cycles of gonadotrophins and 3 cycles of IVF. Obviously, the effectiveness of CC and FSH in these long treatment protocols needs to be confirmed in randomized clinical trials. We are currently performing such a trial. (NTR1449) Until such trials are completed, we propose that continuation of 6 cycles of CC after 6 cycles of CC, followed by gonadotrophins should be the treatment of choice recommended by the guidelines.
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