Individualized cost-effective conventional ovulation induction treatment in normogonadotrophic anovulatory infertility (WHO group 2)


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study examined the use of the anti-oestrogen clomiphene citrate (CC), exogenous gonadotrophins (follicle-stimulating hormone, FSH) and in-vitro fertilisation (IVF) used in sequence to treat anovulatory infertility (WHO group 2).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The hypothetical study population comprised women with WHO 2 anovulatory infertility.

Setting
The setting was secondary care. The economic study was carried out in the Netherlands.

Dates to which data relate

Source of effectiveness data
The effectiveness data were derived from two published studies. The majority of the effectiveness data were derived from a cohort of 240 consecutive patients with WHO 2 anovulatory infertility, details of which have been reported elsewhere (Eijkemans et al. 2003, see ‘Other Publications of Related Interest’ below for bibliographic details).

Link between effectiveness and cost data
The resource use data for CC and FSH were derived from the same patient sample used to determine the effectiveness of CC and FSH.

Modelling
Deterministic prediction models were built to estimate the cost per successful pregnancy with each of the different treatment algorithms, for each of the 16 prognostic groups. It was assumed that the efficacy of each of the treatment options remained the same, regardless of the order of treatment.
Outcomes assessed in the review
The outcomes assessed were:

the probability of pregnancy with CC, FSH and IVF;

the probability of clomiphene-resistant anovulation; and

the probability of spontaneous pregnancy.

Study designs and other criteria for inclusion in the review
The authors did not design a review. The study required prediction models for the probability of pregnancy following CC, FSH and IVF. The probabilities for CC and FSH were based on a single study. Since no predictors for pregnancy following IVF were available from that single study, the prognosis with IVF was based on the Templeton model (Templeton et al. 1996, see ‘Other Publications of Related Interest’ below for bibliographic details). The authors used a third study to provide a model to predict spontaneous pregnancy.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Three primary studies were included in the effectiveness review.

Methods of combining primary studies
The individual patient level data from the patient cohort described in Eijkemans et al. (2003) were re-analysed for the purpose of this study. The model from Templeton et al. was extracted and adjusted to current live-birth rates and current average number of cycles, using published data from the national Dutch IVF registration. The model for spontaneous pregnancy was adapted, assuming that the prediction for women with ovulation disorder was based on the same mix of amenorrhoeic and oligomenorrhoeic women as the study by Eijkemans et al.

Investigation of differences between primary studies
Not reported.

Results of the review
The authors did not report the individual effectiveness parameters for CC and FSH.

The chances of pregnancy with IVF were estimated to be 24% for women under 30 years old and 19% for women over 30.

The probability of spontaneous pregnancy for oligomenorrhoeic women was estimated to be 26% for women under 30 years old and 15% for women over 30.
Measure of benefits used in the economic analysis
The outcome measure for the economic analysis was the number of ongoing pregnancies.

Direct costs
The study included direct costs to the health service. The direct costs included the costs of CC, recombinant FSH, HCG (human chorionic gonadotrophin), lesson in self injection, outpatient clinic visits, progesterone assessment, ultrasonography, pregnancy tests and IVF. The cost and resource use data were extracted from published studies and used to calculate the average cost of treatment with CC, FSH and IVF. These were then used in the prediction model to calculate the costs of each of the treatment strategies examined. The study reported the costs and the resource quantities separately. The source of the unit costs was unclear. It was unclear whether discounting was relevant as the authors did not discuss the time horizon for the model; the costs did not appear to have been discounted. The study reported the average costs. The costs were updated to the price year 2002 using an accumulated rate of inflation.

Statistical analysis of costs
Resource use and cost data were treated as point estimates although patient level data was available for some of the resource use parameters.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Euros (EUR).

Sensitivity analysis
The authors conducted a sensitivity analysis using higher published cost estimates for treatment with FSH.

Estimated benefits used in the economic analysis
The strategy of CC+FSH+IVF was estimated to result in a pregnancy chance of between 39.4% and 76.0%, depending on prognostic group. The strategy of FSH+IVF produced lower pregnancy chances in most prognostic groups, with the difference from CC+FSH+IVF ranging from -10.1% to +5.3%. The strategy of CC+IVF resulted in lower pregnancy chances for all prognostic groups compared with CC+FSH+IVF, with the difference ranging from -8.0% to -0.5%. Complications from treatment were not included explicitly in the analysis.

Cost results
The average cost of treatment was estimated to be EUR 233 with CC, EUR 4,497 with FSH and EUR 3,843 with IVF.

Synthesis of costs and benefits
The costs and benefits were combined to calculate the cost per ongoing pregnancy. The authors performed an incremental analysis, comparing each treatment strategy to the reference strategy of CC+FSH+IVF.

The strategy of FSH+IVF was dominated by the reference strategy in all but three prognostic groups. The cost-effectiveness ratio exceeded the threshold of EUR 10,000 per pregnancy in those prognostic groups.

The strategy of CC+IVF was found to be cost-effective in women over 30 and women under 30 with elevated androgen levels. For women under 30 with normal androgen levels, the cost-effectiveness ratio for the reference strategy compared with CC+IVF was EUR 7,206 per pregnancy.
At each stage of treatment, including not starting treatment at all, there were some prognostic groups for whom the continuation of treatment was not cost-effective at a threshold of EUR 10,000 per pregnancy.

The results were sensitive to the alternative estimates of the treatment costs of FSH.

Authors’ conclusions
Follicle-stimulating hormone (FSH) should be skipped in women over 30 years old and women under 30 with elevated androgen levels. The authors stated that they could not conclude that stopping treatment was efficient for any prognostic group, as the chances of spontaneous pregnancy would most likely be lower in treatment failures and this was not accounted for in the model.

CRD COMMENTARY - Selection of comparators
The authors selected to compare variations of the conventional treatment strategy for anovulatory infertility with the reference strategy of CC+FSH+IVF, which was current practice in the study setting. You must decide whether this represents conventional treatment in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness data were derived from published studies. The authors did not state that a systematic review of the literature was undertaken, instead they supplemented a series of patient level data they had access to with additional studies from the literature. Given this fact, it was difficult to ascertain whether the best available evidence had been used to populate the model. The prediction models for CC, FSH and IVF from the patient level data and the published studies were combined to create a prediction model for treatment strategies. The authors did not consider the impact of differences between the studies on the validity of their prediction model. The authors acknowledged that the assumption that the efficacy of each individual treatment option was independent of its order in the treatment strategy was an important one.

Validity of estimate of measure of benefit
The estimation of ongoing pregnancies was modelled. The authors acknowledged that they did not consider the differences between singleton and multiple pregnancies.

Validity of estimate of costs
The authors did not state the cost perspective of the study, but they stated that they included the direct medical costs. The authors included all the relevant categories of direct costs for treatment, but they did not include the cost made during pregnancy or delivery. They acknowledged that the inclusion of these costs would favour FSH over IVF, as IVF results in a higher proportion of multiple pregnancies. The costs and the quantities were reported separately, which improves the generalisability of the study results, but the authors did not clearly report the source of the unit cost data. Some patient level data on resource use were available, but none of the data were analysed stochastically. The authors stated that their estimated cost of FSH was lower than other recently published studies, and they performed a sensitivity analysis on the published estimates. The costs were adjusted to the price year 2002, but it was unclear whether discounting was relevant or undertaken.

Other issues
The authors stated that there are few existing economic evaluations of treatment for anovulatory infertility, although they managed to compare their results with some published studies. The authors acknowledged that their prediction models had not been externally validated, but did not discuss further the generalisability of the study results. They stated that the method might be generalisable to other settings. The authors presented full results for only a sub-set of the strategies they investigated.
Implications of the study
The authors stated that further studies should be designed to validate the prediction model. The also stated that any similar health economic studies should include alternative treatment strategies and the cost of multiple pregnancies.

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None stated.

Bibliographic details

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Other publications of related interest


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