Comparison of outcomes and direct cost between minimal stimulation and conventional protocols on ovarian stimulation in in vitro fertilization

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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 a minimal stimulation protocol (MIN) with clomiphene and gonadotropin for ovarian stimulation in in-vitro fertilisation (IVF). MIN consisted of either clomiphene citrate and human menopausal gonadotropin (hMG) or recombinant gonadotropin. Clomiphene citrate was given for 5 days at a dosage of 50 - 150 mg/day, starting from day 3 of the menstrual cycle. hMG (75 - 150 IU/day) or recombinant gonadotropin was started after the last day of clomiphene citrate administration until the leading follicle reached a diameter of 18 mm. Thereafter, patients were injected once with human chorionic gonadotropin (hCG) in a single dose of 10,000 IU.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised infertile patients undergoing IVF. Patients with polycystic ovaries or male factor infertility who needed intracytoplasmic sperm injection procedure were excluded.

Setting
The setting was a hospital. The economic study was carried out in Thailand.

Dates to which data relate
The effectiveness and resource use data were gathered from July 1996 to March 2003. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing appears to have been carried out prospectively on the sample of patients included in the effectiveness study.

Study sample
Power calculations, if performed, were not reported. A sample of 192 patients was enrolled. There were 96 cases in each group. The mean age of the sample was 35 years. Endometriosis was the most common cause of infertility (28.1%), followed by unexplained infertility (27.1%) and tubal factor (22.9%).
Study design
This was a prospective cohort study that was carried out at a single institution, the Infertility and Assisted Reproductive Unit, Ramathibodi Hospital, Faculty of Medicine, Mahidol University in Thailand. The length of follow-up was not stated. No patient was lost to the follow-up assessment.

Analysis of effectiveness
All of the patients included in the initial study sample were considered in the analysis of effectiveness. The clinical outcomes used were:

- the oocyte number;
- the fertilisation rate;
- the cleavage rate;
- the average cumulative embryo score (ACES);
- transferred embryos;
- the pregnancy rates per retrieval cycle, per embryo transfer and per patient;
- time of ovarian stimulation;
- dose of gonadotropin; and
- the rate of cancelled cycles.

A clinical pregnancy was defined by the presence of a gestational sac on ultrasonic examination. The method used to calculate the ACES was described. The study groups were comparable at baseline since the two groups were matched for age and cause of infertility.

Effectiveness results
The mean number of oocytes was 4.5 (+/-3.3) in the MIN group and 7.3 (+/-4.9) in the CON group, (p=0.000).

The fertilisation rate was 73.4 (+/- 31.9) in the MIN group versus 69.3 (+/- 29.6) in the CON group, (p not significant).

The cleavage rate was 84.9 (+/- 32.6) in the MIN group versus 88.4 (+/- 28.0) in the CON group, (p not significant).

The median ACES score was 12 (range: 0 - 28.4) in the MIN group versus 10 (range: 0 - 22.0) in the CON group, (p not significant).

The mean number of transferred embryos was 2.3 (+/- 1.5) in the MIN group versus 2.8 (+/- 1.6) in the CON group, (p=0.024).

The pregnancy rate per retrieval cycle was 13.1% in the MIN group versus 13.0% in the CON group, (p not significant).

The pregnancy rate per embryo transfer was 14.5% in the MIN group versus 14.0% in the CON group, (p not significant).

The pregnancy rate per patient was 13.3% in the MIN group versus 13.2% in the CON group, (p not significant).

The mean time of ovarian stimulation was 8.1 (+/-0.6) days in the MIN group versus 10.0 (+/-1.8) days in the CON group, (p=0.000).

The mean dose of gonadotropin was 633.9 (+/-299.5) units in the MIN group versus 2,172.2 (+/-808.8) units in the
CON group, (p=0.000).

The rate of cancelled cycles was 12.5% in the MIN group versus 4.2% in the CON group, (p not significant).

**Clinical conclusions**
The effectiveness analysis showed that the two protocols produced several comparable outcomes. However, CON gave more oocyte numbers and fewer transferred embryos than MIN. As expected, MIN led to a shorter time of ovarian stimulation and a lower dose of gonadotropin.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the pregnancy rate. This was derived directly from the effectiveness analysis.

**Direct costs**
The cost/resource boundary of the study was not explicitly stated. The analysis of the costs included the hormonal medication used during ovarian stimulation, clomiphene citrate, gonadotropin, GnRHa, hormonal medication used during luteal support after embryo transfer, and operative and laboratory costs. The unit costs were not presented separately from the quantities of resources used. Resource use was estimated from the sample of patients included in the effectiveness study. The source of the costs was not stated, but it appears to have been the authors’ institution. Discounting was not relevant as the costs were incurred during a short time. The price year was not stated.

**Statistical analysis of costs**
Student’s t-test was used to test the statistical significance of differences in total costs between the groups.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
US dollars ($).

**Sensitivity analysis**
Sensitivity analyses were not carried out.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
The mean cost per cycle was $693.4 (+/- 161.3) with MIN and $1,376.8 (+/- 363.4) with CON, (p=0.000).

**Synthesis of costs and benefits**
The average cost-effectiveness ratios were calculated to combine the costs and benefits of the alternative stimulation protocols.

The median cost per pregnancy was $6,021.9 (range: 4,235.1 +/- 9,045.2) with MIN and $10,785 (range: 7,868.2 +/- 12,366.7) with CON, (p=0.000).
Authors' conclusions
The minimal stimulation protocol (MIN) was less effective than the conventional stimulation protocol (CON) for ovarian stimulation in in-vitro fertilisation (IVF) in Thailand. However, its low cost might justify further evaluation of its role in the treatment of infertility in specific cases.

CRD COMMENTARY - Selection of comparators
The choice of the comparator was justified on the grounds that it was a conventional stimulation protocol. A detailed description of the two stimulation protocols was provided. You should decide whether the CON is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness analysis was based on a cohort study, but a randomised trial would have been more appropriate to reduce potential selection bias and confounding factors. In fact, the authors stated that there might have been some selection bias, such as lower stage endometriosis in the MIN group, which might have led to similar pregnancy rates in the two treatment groups. The baseline comparability of the study groups was not discussed but was ensured by the fact that the groups were matched. The evidence came from a single institution, which could limit how representative the patient sample was. The size of the sample was not justified statistically, and this could explain the lack of statistical significance of differences observed between the groups for most clinical outcomes. These issues tend to limit the internal validity of the study.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. It would not be comparable with the benefits of other health care interventions. The impact of the interventions on quality of life was not investigated.

Validity of estimate of costs
The perspective adopted in the study was not stated and a detailed breakdown of cost items was not reported. The cost analysis was restricted to those costs relevant to the stimulation protocol. The costs associated with other aspects of care, such as the treatment of adverse events or cancellation of cycles, were not taken into account. Information on the unit costs and quantities of resources used was not presented separately, which limits the possibility of replicating the cost analysis in other settings. Conventional statistical analyses of the costs were carried out, but the cost estimates were specific to the study setting. The impact of using alternative cost estimates was not investigated. The source of the costs was not stated and the price year was not reported. This will hinder reflation exercises in other time periods.

Other issues
The authors reported the results from a few published studies but did not compare them directly with the findings of the current study. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not performed, which limits the external validity of the analysis. The study referred to infertile patients undergoing ovarian stimulation in IVF and this was reflected in the authors' conclusions.

Implications of the study
The study results suggested that MIN might be used for specific cases, such as patients with financial constraints.

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None stated.

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**Other publications of related interest**


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