Minimal stimulation protocol for use with intrauterine insemination in the treatment of infertility

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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 use of two protocols for ovarian stimulation in infertile couples undergoing intrauterine insemination after clomiphene citrate (CC) failure. The protocols compared were minimal stimulation versus full stimulation. Under the minimal stimulation protocol, women were given 100 mg CC during cycle days 3 to 7, followed by a single injection of 150 IU human menopausal gonadotrophin (hMG). The full protocol consisted of 100 mg/day CC on days 3 to 7 and 75 to 150 IU/day hMG on days 5 to 9, while further hMG dosage was adjusted according to follicular monitoring.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised couples suffering from idiopathic or unexplained infertility and undergoing intrauterine insemination. In particular, the following inclusion criteria were considered:

- infertility of at least 2 years;
- normal history and physical examination;
- adequate coital frequency;
- normal semen analysis;
- regular ovulatory menstrual cycles;
- adequate cervical mucus and a normal postcoital test;
- normal levels of follicle stimulating hormone, leutinising hormone, prolactin, and thyroid stimulating hormone;
- normal hysterosalpingography and/or laparoscopy.

The criteria for CC failures were anovulatory women who ovulated with CC but fail to conceive in 5 or 6 cycles, and women with unexplained infertility who had been given CC empirically.

Setting
The setting was tertiary care. The economic study was conducted in India.
Dates to which data relate
The effectiveness and resource use data were gathered from May 1998 to April 2000. 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 was conducted prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
The use of power calculations was not reported. A sample of 200 women undergoing intrauterine insemination at the authors’ institution was recruited. The methods used to select the sample were not described. There were 100 patients in each group. The mean age was 28.45 (+/- 4.23) years in the minimal stimulation group (216 treatment cycles) and 30.03 (+/- 4.62) years in the full stimulation group (204 treatment cycles).

Study design
This was a prospective, randomised clinical trial that was conducted in a single centre, the Department of Obstetrics and Gynaecology of Nehru Hospitals in Chandigarh. The patients were allocated to the study groups using a random table before starting the first cycle of ovarian stimulation. The length of follow-up was not reported. No loss to follow-up was observed. The outcome assessment was not blinded.

Analysis of effectiveness
The analysis of effectiveness appears to have been conducted on an intention to treat basis, as all the patients included in the initial study sample were accounted for in the effectiveness study. The outcomes estimated in the analysis were:

- the number of dominant follicles,
- the number of visits for monitoring,
- the number of ampoules of hMG (75 IU),
- the pregnancy rate per couple and per cycle,
- the rate of abortion,
- the rate of multiple gestation,
- the incidence of hyperstimulation.

The two groups were comparable in age, years of infertility, type of infertility, or indication for treatment.

Effectiveness results
There were 1.83 (+/- 0.71) dominant follicles in the minimal stimulation group versus 3.16 (+/- 1.50) in the full stimulation group.

There was 1 visit for monitoring in the minimal stimulation group versus 3.15 (+/- 1.21) in the full stimulation group.

The number of ampoules of hMG (75 IU) was 2 in the minimal stimulation group versus 12 (+/- 5.4) in the full stimulation group, (p<0.01).
The pregnancy rate per couple was 35% in the minimal stimulation group versus 39% in the full stimulation group.
The pregnancy rate per cycle was 16.20% in the minimal stimulation group versus 19.12% in the full stimulation group.
The rate of abortion was 5.7% in the minimal stimulation group versus 23% in the full stimulation group, (p<0.05).
The rate of multiple gestation was 0% in the minimal stimulation group versus 5.13% in the full stimulation group.
The incidence of hyperstimulation was 0% in the minimal stimulation group versus 3% in the full stimulation group.

Clinical conclusions
The effectiveness study showed that minimal and full simulations led to comparable pregnancy rates. However, significantly fewer abortions were observed with the minimal stimulation protocol.

Measure of benefits used in the economic analysis
The health outcomes were left disaggregated and no summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was conducted.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs were presented separately for most items. The health services included in the economic evaluation were CC, hMG, human chorionic gonadotrophin and monitoring. The cost/resource boundary of the study was unclear, but it could have been that of the medical centre. Resource use was estimated using actual patient-level data derived from the sample of couples involved in the effectiveness analysis. The medication costs came from market prices. The price year was not reported.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
US dollars ($).

Sensitivity analysis
Sensitivity analyses were not conducted.

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

Cost results
The total costs per cycle were $63.50 with minimal stimulation and $216.50 with full stimulation.

The main cost difference was in the cost of hMG. HMG cost $27.00 in the minimal stimulation group and $162.00 in the full stimulation group.
Synthesis of costs and benefits
A synthesis of the costs and benefits was not relevant since, in effect, a cost-consequences analysis was conducted.

Authors' conclusions
The minimal stimulation protocol was as effective as a full stimulation procedure in women with unexplained infertility who were undergoing intrauterine insemination. It led to a substantial reduction in the treatment costs and required minimal monitoring, which was appealing to both the patients and clinicians.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Full stimulation along with intrauterine insemination represented a standard protocol for ovarian stimulation. You should decide whether it is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness was based on a clinical trial, which was appropriate for the study question. The method of randomisation was reported, but no information on the methods of sample selection and outcome assessment was given. The study groups appear to have been comparable at baseline in terms of their demographics and clinical characteristics. Statistical tests were conducted when the outcomes were compared. The main limitation of the study was the fact that no justification for the appropriateness of the sample size was provided and no power calculations were reported. Further, the evidence came from a single centre. Some assessment bias may have been introduced as blinding was not used. These issues partially limit the internal validity of the analysis.

Validity of estimate of measure of benefit
No summary benefit measure was used in the analysis because, in effect, a cost-consequences analysis was conducted.

Validity of estimate of costs
The perspective adopted in the study was not explicitly stated, although it could have been that of the medical centre. However, in some settings, these costs could have been borne by the patients. The inclusion of other costs, such as the treatment of hyperstimulation, would have been interesting but would not have changed the conclusions of the analysis. The unit costs were reported separately from the quantities of resources used for some items. The price year was not reported, although the authors mentioned the period during which the quantities of resources used were collected. The cost estimates were specific to the study setting and no sensitivity analyses were conducted. Similarly, no statistical tests were conducted to test the statistical significance of differences in the costs. However, the cost-difference was substantial.

Other issues
The authors made some comparisons of their findings with those from other studies. It was noted that wide ranges of pregnancy rates were reported in the literature. The issue of the generalisability of the study results to other settings was not addressed and sensitivity analyses were not conducted. Therefore, the external validity of the analysis was low. The study involved women suffering from idiopathic or unexplained infertility and this was reflected in the conclusions of the analysis.

Implications of the study
The study results suggested that a protocol of minimal stimulation should be offered to unexplained and CC failure cases before starting a conventional stimulation regime or more complex, assisted reproductive techniques.

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