Letrozole versus human menopausal gonadotrophin in women undergoing intrauterine insemination
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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 letrozole, one of a new class of drugs known as aromatase inhibitors, in women undergoing intrauterine insemination (IUI). This intervention was compared with the use of human menopausal gonadotrophin (HMG).

Women undergoing ovarian stimulation and IUI, for whom no ovarian cyst was seen on the sonogram, were given letrozole 5 mg/day (Femara; Novartis) from day 3 to day 7 of the menstrual cycle. In the comparator group of women, either 75 IU (women younger than 30 years) or 150 IU (women aged 30 and older) of intramuscular HMG (Menagon; Ferring) were given daily from day 3 for 5 days. After 5 days, the dose and duration of HMG treatment were adjusted according to the patient's response to treatment. Patients in both groups were monitored every other day after day 7 of the menstrual cycle by transvaginal ultrasound and by measurement of oestradiol and luteinising hormone (LH) blood concentrations.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The population comprised couples with unexplained infertility. The patients had regular menstrual cycles of 26 to 34 days, a pelvic ultrasound showing normal size and structure of uterus and ovaries, a hysterosalpingogram and/or laparoscopy showing tubal patency, thyroid and reproductive hormones within the normal range. The semen to be used was acceptable according to World Health Organisation guidelines. The women had already undergone at least one ovulation induction treatment cycle combined with intercourse, but had not undergone an IUI cycle before.

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

Dates to which data relate
The dates of the effectiveness and resource evidence were not given. No price year was given.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same patients who provided the effectiveness data.
Study sample
Power calculations were performed retrospectively. A statistical power of 6% at a probability of about 0.05 with a study sample of 80 patients (40 in each group) was reported. However, the authors did not state to which difference between the groups the statistical power referred. The study sample consisted of couples with fertility problems attending a particular hospital who met the inclusion criteria.

Study design
This was a single-centre, randomised controlled trial (RCT) in which couples were randomly assigned to one of two treatment groups according to a computer-generated randomisation list. The specialist who performed the IUI was blinded to the woman's treatment group. It was unclear whether the patients were followed up after the initial month when pregnancy could be established.

Analysis of effectiveness
The analysis was conducted on an intention to treat basis. The primary health outcome used was the pregnancy rate. The secondary health outcomes were thickness of the endometrium, length of the follicular phase, premature LH surge frequency, number of pre-ovulatory follicles (>14 mm in diameter) and complications. The two groups were comparable in terms of their age and basic characteristics of infertility (i.e. diagnostic parameters, cause and duration of infertility).

Effectiveness results
The pregnancy rate was 18.42% in the letrozole group and 15.78% in the gonadotrophin group, (p not significant).

The number of follicles >14 mm was lower in the letrozole group than in the HMG group (1.79 +/- 1.3 versus 3.21 +/- 1.6; p<0.001).

The oestradiol concentrations were considerably higher in the HMG group than in the letrozole group (875.15 +/- 368 versus 193.19 +/- 80; p<0.001).

There was no difference in endometrial pattern between the two groups.

The length of stimulation was longer in the letrozole group than in the HMG group (12.77 +/- 1.9 versus 11.90 +/- 1.7 days; p=0.034).

The difference in LH concentrations between the two groups was not statistically significant.

There was one moderate case of ovarian hyperstimulation syndrome in the gonadotrophin group.

There was one case of triplets in the letrozole group and one case of twins in the gonadotrophin group.

Clinical conclusions
There was no difference in pregnancy rates between the two patient groups. Hence, there was no clinical reason to favour one of the two treatments.

Measure of benefits used in the economic analysis
No summary measure of benefit was used as the authors carried out a cost-consequences analysis.

Direct costs
Discounting was not carried out as the costs were incurred during less than 2 years. The costs of HMG and letrozole were calculated. The unit costs and the quantities were analysed separately. No other costs were included. The costs
were estimated on the basis of actual data obtained from the hospital. No price year was given.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were estimated.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was carried out.

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

**Cost results**
The cost per cycle was $43 in the letrozole group and $225 in the gonadotrophin group, (p<0.001).

The costs of adverse effects were not dealt with in the costing. The cost-advantage in the letrozole group would have been even larger if the cost of ovarian hyperstimulation syndrome had been included. It seems that the costs for the first month have been included.

**Synthesis of costs and benefits**
The costs and benefits were not combined as the study was a cost-consequences analysis.

**Authors' conclusions**
Both treatments were equally effective but the letrozole treatment was much cheaper. Therefore, "letrozole offers a new treatment regimen in ovarian stimulation regimens for intrauterine insemination (IUI) that is cost-effective, simple and convenient for the patients".

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator, HMG, was justified as it represents current practice in many settings. You should decide if this represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The source of the effectiveness data was a single study. The study design, an RCT, was appropriate for the hypothesis. The study sample was representative of the study population. The patient groups were shown to be comparable at analysis. The analysis of effectiveness was handled credibly. Power calculations were reported. However, the authors acknowledged that the power was low and, therefore, it is not possible to ascertain whether the results obtained were due to the intervention or to chance. The method of randomisation was reported, as was blinded assessment, suggesting that the internal validity of the study is likely to be good. There were no other sources of effectiveness data.
Validity of estimate of measure of benefit
The authors did not derive a summary measure of health benefit as they carried out a cost-consequences analysis.

Validity of estimate of costs
Given the cost perspective adopted, it was unclear whether all the relevant cost categories were included. It appears that the cost-difference would be greater than that shown in the study, as letrozole does not require injections (unlike HMG). Also, if there were costs resulting from ovarian hyperstimulation syndrome that had been included, the cost-advantage to letrozole would be even greater. The costs that were included were broken down into costs and quantities. The resource use quantities were taken from a single study, while the prices were taken from the authors' setting. No other sources of prices were used. No statistical, sensitivity or any other kind of analysis of the quantities or prices was undertaken. No price year was reported, which will hinder any future inflation exercises. Discounting was not relevant as the costs were incurred during less than 2 year.

Other issues
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively and their conclusions reflected the scope of the analysis. The authors described the trial as a pilot study and acknowledged its low statistical power. They did not report any other limitations of their study.

Implications of the study
The authors appear certain that their study shows that letrozole is superior on the grounds of cost and has similar pregnancy outcomes to HMG. A study with larger statistical power would be helpful to support this conclusion. Also, more detailed information on the costs and cost sources would be helpful in determining whether the lower costs of letrozole treatment prevailed over a variety of settings and for a range of prices.

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