Agonist versus antagonist in ICSI cycles: a randomized trial and cost effectiveness analysis
Badrawi A, Zaki S, Al-Inany H, Ramzy A M, Hussein M

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 two protocols for controlling ovarian simulation in in vitro fertilisation (IVF) or intracytoplasmic sperm injection cycles. A long protocol of gonadotrophin-releasing hormone (GnRH) agonist (Suprefact, Hoechst Marrion Roussel) plus human menopausal gonadotrophin (hMG; Menogon, Ferring) was compared with a flexible protocol of GnRH antagonist (Ganirelix 0.25 mg) plus hMG.

In the first intervention (GnRH agonist-hMG), the GnRH-agonist was administered as a nasal spray (600 g/day, divided into 6 daily doses). Administration started in the mid luteal phase of the cycle preceding the treatment cycle, and continued until the day human chorionic gonadotropin (hCG) was given. Estradiol was given 14 days later to confirm downregulation and then hMG was administered (225 IU).

In the second intervention (hMG-GnRH antagonist), hMG was first administered on the second day of the cycle, 3 ampoules (225 IU Menogon) daily. Ganirelix 0.25 mg was administered subcutaneously daily, starting from when the lead follicle measured 14 mm up to and including the day of hCG administration.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised primary infertility patients, aged 18 to 39 years old. The patients had regular menstrual cycles, follicle stimulating hormone (FSH) levels of less than 10 IU/L (as measured at cycle day 3) and ultrasound examination showing normal uterus. Women with severe endometriosis (American Fertility Stage III and IV) and azoospermic males were excluded from the study.

Setting
The study setting was secondary care. The economic study was carried out in Cairo, Egypt.

Dates to which data relate
The dates to which the effectiveness and resource use data related were not reported. The price year was not reported.

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

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

**Study sample**
No sample size was determined in the planning phase of the study. The authors reported that no power calculations were performed since a large number of patients would be required to detect statistically significant differences between the two groups. Of the 100 couples recruited from an IVF unit, 50 patients received the GnRH agonist "long luteal protocol"-hMG and 50 received the hMG-GnRH antagonist flexible protocol. The mean age of the patients was 30.28 years (standard deviation, SD=5.19) in the GnRH agonist-hMG group and 30.81 years (SD=4.8) in the hMG-GnRH antagonist group.

**Study design**
The study was a randomised controlled trial (RCT) that was conducted in a single centre. The women were randomised using sealed envelopes. The duration to follow-up was not reported. The authors reported that 3 patients in the group receiving hMG-GnRH antagonist discontinued treatment because of poor response. The authors did not report whether the patient or clinician were blinded to the type of treatment being administered.

**Analysis of effectiveness**
The analysis of the clinical study was conducted on the basis of treatment completers only. The outcomes used were:
- the duration of stimulation;
- the number of follicles;
- the size of the follicles;
- the endometrial thickness;
- the number of oocytes retrieved;
- the number of MII oocytes;
- the number of oocytes fertilised;
- the fertilisation rate;
- the number of embryos;
- the number of transferred embryos;
- the pregnancy rate;
- the abortion rate; and
- the number of OHSS (not defined).

The patients were shown to be comparable in terms of age, infertility duration and baseline FSH. However, patients receiving hMG-GnRH antagonist were found to have statistically significant higher levels of LH at day 3, (p=0.043), and E2 levels at day 14, (p=0.003) and on the day of hCG administration, (p<0.001).

**Effectiveness results**
hMG use was 36.88 ampoules (SD=7.77) in the GnRH agonist group versus 34.09 ampoules (SD=3.35) in the GnRH antagonist group, (p=0.025).
The duration of stimulation was 11.42 days (SD=2.31) in the GnRH agonist group versus 10.32 days (SD=1.38) in the GnRH antagonist group, (p=0.005).

The number of follicles was 16.34 (SD=7.77) in the GnRH agonist group versus 11.83 (SD=5.59) in the GnRH antagonist group, (p=0.001).

The number of oocytes retrieved was 12.6 (SD=6.15) in the GnRH agonist group versus 9.68 (SD=5.28) in the GnRH antagonist group, (p=0.014).

The number of MII oocytes was 10.46 (SD=5.25) in the GnRH agonist group versus 8.26 (SD=4.96) in the GnRH antagonist group, (p=0.036).

The number of oocytes fertilised was 7.88 (SD=4.15) in the GnRH agonist group versus 6.38 (SD=3.05) in the GnRH antagonist group, (p=0.047).

The fertilisation rate was 77.7% in the GnRH agonist group versus 82.5% in the GnRH antagonist group, (p=0.179).

The number of embryos was 7.78 (SD=4.2) in the GnRH agonist group versus 6.11 (SD=3.1) in the GnRH antagonist group, (p=0.029).

The number of transferred embryos was 2.68 (SD=0.81) in the GnRH agonist group versus 2.4 (SD=1.01) in the GnRH antagonist group, (p=0.015).

There were 15 (30%) conception cycles in the GnRH agonist group, including two miscarriages (13.3%) at a mean of 5.5 weeks' gestation. This resulted in 13 deliveries of healthy children. In the GnRH antagonist group, there were 12 (25.5%) conception cycles with one miscarriage (8.3%) at 5 weeks' duration. This resulted in 12 healthy children born. These differences were not statistically significant.

The pregnancy rate per attempt was 30% in the GnRH agonist group and 24% in the GnRH antagonist group, (p=0.625).

**Clinical conclusions**
The use of GnRH antagonists resulted in shorter duration of simulation and a reduction in hMG use. However, the pregnancy rates and the number of deliveries of healthy children were not statistically different between the two groups.

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

**Direct costs**
The direct costs included in the analysis were those to the hospital. These comprised the costs of medication (i.e. hMG, GnRH agonist, GnRH antagonist) and the costs of luteal phase support. The authors did not report the sources used to derive the costs of medication. Discounting was not necessary, as all the costs were incurred during a short time, and was not performed. The study reported the mean costs. The price year was not reported.

**Statistical analysis of costs**
The costs were treated stochastically. P values of less than 0.05 were considered significant.

**Indirect Costs**
The indirect costs were not included.
Currency
Egyptian pounds (EGP).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
The pregnancy rate was 30% in the GnRH agonist group and 24% in the GnRH antagonist group, (p=0.657).

Cost results
The total mean cost per cycle was EGP 9,240 in the GnRH agonist group and EGP 9,640 in the GnRH antagonist group, (p<0.05).

Synthesis of costs and benefits
The costs and benefits were combined using an average cost-effectiveness ratio (i.e. the cost per pregnancy).

The cost per pregnancy was EGP 40,166 in the GnRH antagonist group and EGP 30,800 in the GnRH agonist group, (p<0.05).

Authors' conclusions
The use of gonadotrophin-releasing hormone (GnRH) antagonists resulted in shorter duration of stimulation and a reduction in human menopausal gonadotrophin (hMG) use. However, the use of GnRH agonists was more cost-effective.

CRD COMMENTARY - Selection of comparators
The authors did not explicitly report why they had chosen GnRH agonists as the comparator. However, this intervention appears to have been current practice in the authors' settings. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on an RCT. This was appropriate for the study question, as well-conducted RCTs are considered to be the 'gold' standard study design when comparing health interventions. The study sample appears to have been representative of the study population. The patient groups were not shown to be comparable in terms of baseline LH and E2 levels. No statistical analyses were undertaken to account for potential biases and confounding factors, and the authors gave no explanation on how these differences might have biased the results from the clinical study. The authors undertook appropriate statistical analyses to test for statistically significant differences between the two groups. However, as they reported, the study was not sufficiently powered to detect differences in outcomes between the two groups. The authors did not define many of the abbreviations used in their report, thus some readers may find it difficult to understand the study.

Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis.

Validity of estimate of costs
The authors undertook a very limited costing, only including the costs of medications and luteal phase support. Other relevant costs, such as those of complications, abortion or pregnancy, were not included in the analysis. It was unclear if
such omissions would have affected the authors’ results. The costs and the quantities were reported separately. However, these were not reported very clearly, and it was not possible to determine how the authors estimated the total costs reported in the paper. The authors did not report the sources used to obtain the unit costs. Appropriate statistical analyses were undertaken to test for statistically significant differences in costs between the two groups. Since the costs were incurred during a short time, discounting was appropriately not performed. The price year was not reported, which will hamper any possible inflation exercises.

Other issues
The authors did not compare their findings with those from other studies. The issue of generalisability to other settings was not addressed. The authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis. The authors did not report any limitations to their study. However, they did not perform an incremental analysis of the costs and benefits. Such an analysis would have found that, in the reference case, the use of GnRH agonists was dominant over the use of GnRH antagonists. The authors could have then used sensitivity analyses to investigate the robustness of this result.

Implications of the study
The authors reported that, although the use of GnRH agonists may not lower the cost of an individual IVF cycle, the observation that its use required fewer cycles to achieve a pregnancy suggests that the total cost of treating a population of patients would be significantly reduced.

Source of funding
None stated.

Bibliographic details

Other publications of related interest


Indexing Status
Subject indexing assigned by CRD

MeSH
Cost-Benefit Analysis; Egypt; Female; Gonadotropin-Releasing Hormone /antagonists & inhibitors /antagonists & inhibitors; Hormone Antagonists; Humans; Infertility, Female /drug therapy; Ovulation Induction /methods; Pregnancy; Pregnancy Rate; Sperm Injections, Intracytoplasmic; Treatment Outcome

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