Clinical consequences of ovarian stimulation in assisted conception and in PCOS
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Chapter 8

Optimizing GnRH antagonist administration: meta-analysis of fixed vs flexible protocol

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Abstract

Objectives: The aim is to investigate whether flexible GnRH antagonist administration according to follicular size would be more beneficial than starting it in a fixed day.

Methods: A comprehensive search strategy was applied including searching Cochrane Menstrual Disorders and Subfertility Review Group specialised register, MEDLINE and EMBASE databases, Hand searching the reference lists of included studies, review and relevant textbooks and abstracts of major international meetings. Only randomised controlled trials in which Subfertile couples undergoing ovulation induction using GnRH antagonist as part of an assisted reproductive cycle were included. The raw data was obtained from each study and summarised in a two-by-two table. The dichotomous data results for each study were expressed as an odds ratio with 95% confidence intervals. These results were combined for meta-analysis with RevMan software (using the Mantel-Haenszel method).

Types of outcome measures: Primary outcomes included pregnancy rate (per woman or per couple) and incidence of premature LH surge. Secondary outcomes included number of oocytes retrieved, amount of antagonist ampoules used, amount of gonadotrophins needed.

Results: Eleven trials were identified but only four RCTs met out inclusion criteria (Ludwig et al, 2001, Kolibianakis et al, 2003, Mochtar et al, 2004 and Escudero et al, 2004). There was no statistically significant difference in pregnancy rate per woman randomized although there was a trend towards a lower pregnancy rate in favor of the fixed protocol especially with delayed administration beyond day 8 O.R 0.7 (95% CI 0.45–1.1). There was no premature LH surge in any participants in both protocols. However, there was statistically significant reduction both in number of antagonist ampoules and amount of gonadotrophins used in the flexible protocol (O.R -1.2 95% CI -1.26–1.15).

Conclusion: there was no statistically significant difference regarding pregnancy rate between flexible & fixed protocols. There was statistically significant reduction in amount of recombinant FSH with flexible protocol.
Introduction

Recently, GnRH antagonists were introduced as a means of prevention of premature LH surge. Unlike the indirect form of pituitary suppression by GnRH agonists, which requires >2 weeks of administration, the GnRH antagonists cause an immediate and direct suppression by competitive binding with the GnRH receptors. GnRH antagonists can therefore be administered just before the expected LH surge and need to be administered only for a few days. The efficacy of the antagonist has been demonstrated by a number of studies.(1-3).

The most commonly used method for administration of the antagonist is on a fixed day (day 6 of gonadotrophin stimulation). This fixed regimen was advised to avoid any risk of premature LH secretion and to simplify stimulation protocol. As there are individual variations in patient response to ovarian stimulation, then a starting GnRH antagonist according to follicular size (flexible protocol) could be of value. The flexible protocol should be based on the follicular size rather than oestradiol level (4). The GnRH antagonist has been found to result in lower oestradiol levels than in agonist cycles (2,3). Therefore, the time of hCG administration needs to be managed through the size of the leading follicle rather than on oestradiol levels.
Results

Eleven trials were identified (5-15). Only four RCTs met out inclusion criteria (6-9). Beloborodov et al trial was excluded although multicenter RCT because it compared flexible protocol based on follicle 14 vs follicle 16 mm (14). Taskin et al, was RCT focusing on endometrial receptivity (15). Other studies were excluded because they were retrospective trials.

There was statistically no significant difference in pregnancy rate per woman randomized although there was a trend towards a lower pregnancy rate in favor of the fixed protocol [O.R = 0.7 95% CI = 0.47 to 1.05]. There was no statistically significant difference in incidence of premature LH surge in both protocols. However, there was statistically significant reduction both in number of antagonist ampoules and amount of gonadotrophins used in the flexible protocol (O.R -1.2 95% CI -1.26- -1.15). There was a trend to an increase in the number of oocytes retrieved with the flexible protocol (OR 1.28 95% CI 0.9-1.6).

Discussion

GnRH antagonists have been used in a fixed regimen in most of the clinical studies published so far. In those regimens, GnRH antagonist was introduced on day 6 of ovarian stimulation regardless of follicular size. Women with a relatively slower follicular recruitment (PCOS, low responders) could be negatively affected by a too early GnRH administration (8).

In addition, the potential direct effects of GnRH antagonists on ovarian function, endometrium and embryo quality are not well known, hence the flexible protocol could reduce the amount of GnRH antagonist consumed per cycle. Whether this reduction would be cost effective, or affects implantation rate, needs to be studied with large sample size. One big advantage of conducting Meta-analysis is pooling the results of studies with similar methodology and addressing the same topic, hence achieving large sample size and tightening the confidence in the results obtained. It was estimated that a sample size of 450 participants would be required to detect a difference of 5% in pregnancy rate and the included trials enrolled 459 participants.
Included studies were truly randomised except Kolibianakis et al, who used a pseudo randomization method (date of birth) (7). Randomization was computer generated in Escudero et al trial (8), using sealed envelopes in Ludwig et al trial (6) and opaque sealed envelopes in Mochtar et al trial (in blocks as per study center)(9). All were single center studies except Mochtar et al, which was multicenter trial. Mochtar et al study received financial support, Kolibianakis et al did not state, and the other two trials did not receive any financial support.

All trials used recombinant FSH for multiple follicular development with starting dose ranged between 150IU (6-7) to 300 IU (8) et al while Mochtar et al (9) used 200IU). Ludwig et al, & Escudero et al, administered GnRH antagonist when the leading follicle was ≥ 14mm (6,8) while Kolibianakis et al, Mochtar et al, administered it when leading follicle was ≥ 15mm (7,9). However, Kolibianakis et al increased the dose of recombinant FSH in the flexible group at the start of the GnRH antagonist which can be considered as a confounder (7). Exclusion of Kolibianakis et al trial (that used a pseudorandomisation technique) did not affect the overall results.

In three studies (7-9) the implantation and pregnancy rates were higher when the antagonist was initiated on a fixed manner (stimulation day 6). It was observed in Mochtar et al trial that patients who received their first GnRH antagonist administration on stimulation day 8 or later, the pregnancy rates decreased remarkably (9). This was further supported by the excluded multicenter RCT (14) that found initiation of GnRH antagonist when leading follicle 14mm is better than 16mm regarding pregnancy rate.

It could be the relatively high LH levels combined with the delayed start of GnRH antagonist is the cause of the negative effect on pregnancy rate, by means of prolonging the E2/LH exposure to the endometrium. This was supported by the excluded study of Bonvantura & Adanyia in which the authors applied the flexible protocol accordingly to LH level rather than follicle size (11). The pregnancy rate in the flexible protocol was twice that in the fixed protocol (43% vs 21.5%). (P= 0.021). The importance of maintaining an intrafollicular environment with LH activity during folliculogenesis to reach proper oocyte maturation has been well documented (16,17).

In conclusion, there was no statistically significant difference regarding pregnancy rate between flexible & fixed protocols. However, there was a trend towards lower pregnancy rate in favor of fixed protocol. There was statistically significant reduction in amount of recombinant FSH with flexible protocol.
In flexible protocol, it is advisable that antagonist administration should not be delayed too far, so that pregnancy rate would not be affected and for prevention of the LH surge to be adequate.
Comparison: 01 pregnancy rate  
Outcome: 01 clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Flexible n/N</th>
<th>Fixed n/N</th>
<th>OR (95%CI Fixed)</th>
<th>Weight %</th>
<th>OR (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudero 2003</td>
<td>20 / 50</td>
<td>26 / 59</td>
<td></td>
<td>25.3</td>
<td>0.85[0.39,1.82]</td>
</tr>
<tr>
<td>Ludwig 2001</td>
<td>7 / 40</td>
<td>4 / 20</td>
<td></td>
<td>7.8</td>
<td>0.85[0.22,3.33]</td>
</tr>
<tr>
<td>Mochtar 2003</td>
<td>23 / 101</td>
<td>34 / 103</td>
<td></td>
<td>45.9</td>
<td>0.60[0.32,1.11]</td>
</tr>
<tr>
<td>kolikianakis 2003</td>
<td>14 / 58</td>
<td>14 / 45</td>
<td></td>
<td>21.1</td>
<td>0.70[0.29,1.68]</td>
</tr>
<tr>
<td>Total(95%CI)</td>
<td>64 / 249</td>
<td>78 / 227</td>
<td></td>
<td>100.0</td>
<td>0.70[0.47,1.05]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.56 df=3 p=0.91
Test for overall effect z=-1.72 p=0.09

Figure 1: comparison between flexible and fixed antagonist protocols (clinical pregnancy rate)
### Comparison: 02 units of gonadotrophin

#### Outcome: 01 amount

<table>
<thead>
<tr>
<th>Study</th>
<th>flexible</th>
<th>Fixed</th>
<th>VMD (95%CI Fixed)</th>
<th>Weight</th>
<th>Fixed (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudero 2003</td>
<td>50 2394.00(874.00)</td>
<td>59 2637.00(1044.00)</td>
<td>0.3 -243.00[603.08,117.08]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ludwig 2001</td>
<td>40 1838.00(576.00)</td>
<td>20 2232.00(624.00)</td>
<td>0.4 -394.00[720.58,67.42]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mochtar 2003</td>
<td>101 1924.00(525.00)</td>
<td>103 1879.00(406.00)</td>
<td>2.5 45.00[83.96,173.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kolikianakis 2003</td>
<td>63 1700.00(50.00)</td>
<td>48 1600.00(60.00)</td>
<td>9.7 100.00[79.01,120.99]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total (95%CI) 254 230 100 95.49[74.85,116.13]

Test for heterogeneity chi-square=12.78 df=3 p=0.0051
Test for overall effect z=9.07 p<0.00001

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Figure 2: comparison between flexible and fixed antagonist protocols (gonadotrophin amount)
Comparison: 01 pregnancy rate
Outcome: 01 clinical pregnancy rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Flexible n/N</th>
<th>Fixed n/N</th>
<th>OR (95%CI Fixed)</th>
<th>Weight %</th>
<th>OR (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escudero 2003</td>
<td>20 / 50</td>
<td>26 / 59</td>
<td></td>
<td>32.0</td>
<td>0.85[0.39,1.82]</td>
</tr>
<tr>
<td>Ludwig 2001</td>
<td>7 / 40</td>
<td>4 / 20</td>
<td></td>
<td>9.8</td>
<td>0.85[0.22,3.33]</td>
</tr>
<tr>
<td>Mochtar 2003</td>
<td>23 / 101</td>
<td>34 / 103</td>
<td></td>
<td>58.2</td>
<td>0.60[0.32,1.11]</td>
</tr>
<tr>
<td>Total(95%CI)</td>
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<td>64 / 182</td>
<td></td>
<td>100.0</td>
<td>0.70[0.45,1.10]</td>
</tr>
</tbody>
</table>

Test for heterogeneity chi-square=0.56 df=2 p=0.76
Test for overall effect z=1.53 p=0.13

Figure 3: comparison between flexible and fixed antagonist protocols (clinical pregnancy rate in truly randomized trials)
References


15. Taskin O, Akkoyunlu G, Akar M, Simsek M, Demir R, Sadik S Comparing the effects of fixed (day 6 start) and flexible start of GnRH antagonist on endometrial receptivity in PCOS. Fertil Steril September 2004 (Vol. 82, Issue (Supplement 2), Page S233)

