The current role of intrauterine insemination for the treatment of male factor and unexplained infertility

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Introduction

For couples with male or unexplained infertility, intrauterine insemination (IUI) is more effective than timed intercourse and cervical insemination (Farquhar et al., 2004). In women with idiopathic infertility IUI in stimulated cycles further improves the pregnancy rate compared with natural cycle IUI (Table 1).

The need for milder ovarian stimulation

The following have a negative impact on IUI outcome:
- duration of infertility
- age of the female partner
- history of pelvic inflammation
- presence of severe male factor(s).

Nevertheless, the most important risk associated with IUI after ovarian stimulation is the incidence of multiple gestation that can be as high as 29% (Gleicher et al., 2000). This is why in the presence of more than three follicles it has been suggested the procedure should be stopped or the cycle converted to IVF, but despite this risk the method is still widely used.

Milder ovarian stimulation methods have been recently introduced in order to reduce the risk of iatrogenic twin pregnancies.

Reduced FSH dose

Simply lowering the follicle stimulating hormone (FSH) dose can give an acceptable rate of pregnancy per cycle (~10%) with a lower rate of twins and triplet (Table 2).

Low dose FSH + antagonist

In a pilot study carried out by our group, the combined use of low-dose recombinant FSH and a GnRH antagonist induced the growth of 1-2 follicles in the vast majority of the cycles (Ragni et al., 2004).

Starting on day 3 of the cycle, patients were given recombinant FSH (Puregon®) 50 IU per day, and the GnRH antagonist Ganirelix (Orgalutran®) at the dose of 0.25 mg per day was started from the day when a leading follicle ≥14 mm in mean diameter was visualized, until HCG administration.

Despite the presence of only one or two follicles IUI produced an unexpectedly high number of clinical pregnancies (11 in 32 cycles).

As unexplained infertility is the best diagnosis for IUI and was the indication for treatment of the majority of patients in this study, this could be the reason for the high rate of pregnancies. Nevertheless, taking into account that in idiopathic infertility after multifollicular ovarian stimulation the expected rate of pregnancy after IUI is 10%,
and considering the small number of mature follicles (1-2), an improvement in the quality of oocytes could be another reason for the success rate.

A better quality of follicles stimulated by low-dose FSH and controlled by the antagonist is also suggested by a recent study in previously poorly responsive ICSI patients (12) observed during a second "spontaneous" ICSI cycle. These women were treated when the follicle reached a diameter of 14-15 mm with low-dose FSH and a GnRH antagonist (for a few days) and the new method of pharmacological treatment normalized the ovarian response, leading to a good normo-responder success rate (Ubaldi et al., in press).

Similarly the use of a GnRH antagonist improved the IVF-ICSI results in patients who had already undergone ovarian hyperstimulation in previous cycles (Somigliana et al., 2004).

To corroborate the findings of the pilot study a multicenter European trial has been recently started and if its results confirm these data the rigid rule of “more oocytes, more pregnancy” will be broken and it will be possible to achieve good clinical results without the unacceptable risk of multiple pregnancies.

REFERENCES


Table 1. Pregnancies after intrauterine insemination: stimulated versus natural cycles (Cohlen and Te Velde, 2002).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>IUI in COH-cycles (pregnancies/cycles)</th>
<th>IUI in natural cycles (pregnancies/cycles)</th>
<th>O.R. (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained infertility (6 studies 1990-2000)</td>
<td>97/1007</td>
<td>52/1069</td>
<td>2.0 (1.4-2.8)</td>
</tr>
<tr>
<td>Male subfertility (5 studies 1990-2000)</td>
<td>40/349</td>
<td>28/337</td>
<td>1.4 (0.86-2.4)</td>
</tr>
</tbody>
</table>

Table 2. Clinical pregnancies in 510 controlled ovarian hyperstimulation* and intrauterine insemination cycles (Healy et al., 2003).

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. (%)</th>
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<tbody>
<tr>
<td>Clinical pregnancies</td>
<td>46 (9% per cycle)</td>
</tr>
<tr>
<td>Births</td>
<td>36 (7% per cycle)</td>
</tr>
<tr>
<td>Twins (+ 1 triplet)</td>
<td>5 (14% of deliveries)</td>
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*FSH 112 IU (day 2-6), then small increments
Intrauterine inseminations (IUI) have been performed since the beginning of the past century for the treatment of infertility. Despite its widespread use, the overall success rate of IUI remains controversial. In general, the most common indications for IUI are unexplained infertility, mild to moderate male-factor infertility, and other cases of infertility in which the woman has an unobstructed genital tract and some ovarian function and the man has motile sperm (1). Other indications that may apply to male factor infertility include; immunological infertility, coital and ejaculatory problems due to different sexual dysfunctions and anatomical defects (2). With the advent of more sophisticated assisted reproductive techniques (ART), offering IUI for infertile couple become a matter of debate. The reported pregnancy rate after IUI showed profound variations in the literature ranging from 0 to over 50% (3). However, many confrontations are challenging the use of IUI on the ground of evidence-based medicine.

The rationale for IUI in the treatment of male subfertility is to increase the density of normal motile spermatozoa at the site of fertilization. Removal of nonmotile spermatozoa, leucocytes and immature germ cells, might contribute to an enhanced sperm quality by a decreased release of lymphokines, cytokines, and free oxygen radicals that may have a negative effect on the fertilizing ability of spermatozoa. On the other hand, the reservoir effect of the cervical mucus and the natural selection of normal fertile spermatozoa are compromised thus decreasing the window of opportunity for sperm oocyte interaction and fertilization. Before insemination, semen has to be processed using one of the established sperm preparation techniques to select a sperm population with best quality. The techniques used for sperm processing vary across the centers worldwide. The most commonly used are the simple wash using various culture media, swim-up, and discontinuous gradient centrifugation (DGC). However, Other less commonly used methods such as; glass bead column, swim-down, and sperm select system have been used in several studies. Despite the diversity in sperm processing techniques, few randomized controlled trials (RCT) could demonstrate a borderline advantage for DGC, while others failed to demonstrate such advantage (4). Large high quality randomized controlled trials, comparing the effectiveness of a gradient and/ or a swim-up and/ or wash and centrifugation techniques on clinical outcome are lacking. Concerning the frequency of insemination some studies favored double insemination (2). On the other hand, double intrauterine insemination showed no significant benefit over single intrauterine insemination (5). In male factor infertility due to impaired semen parameters the results are contradictory. Ideally evidence should be gained from large multi-center well-designed randomized studies in clearly defined populations of subfertile males. Despite

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