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Commentary

Evidence-based follitropin

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Abstract

The proper utilization of gonadotrophin during ovarian stimulation is absolutely essential and can modify the results (pregnancy rates). Moreover, several compounds and preparations are now available for use. This commentary discusses those preparations of follitropin (FbM and FbB) and the most relevant epidemiological evidence to obtain the best result during ovarian stimulation.

Keywords: *FbB, FbM, follitropin, ovarian stimulation, recombinant FSH*

Evidence-based medicine (EBM) was defined during the mid-19th century in Paris with some important and basic philosophical concepts. The practice of EBM means integrating individual clinical expertise with the best available external clinical evidence from systematic research. This concept could be applicable in all fields of medicine and all clinical decisions must be systematically reviewed in order to accept the best evidence.

Sometimes, the best evidence is not the perfect evidence. In clinical practice and consequently in clinical trials, there are several factors and covariates that could interfere some end-points. Furthermore, we have to search for the best evidence observing two important points: the level of evidence and its respective quality. For treatment, for example, the best design is a randomized clinical trial or a systematic review with a meta-analysis. However, if the sample size is insufficient or the measurement method inadequate, the quality and consequently the external extrapolation of the results will be absolutely inadequate.

The paper from Wikland *et al*. (2006) raises a fundamental and crucial question in reproductive medicine: the consistency (quality) of ovarian stimulation. During the last four decades remarkable advances in ovarian stimulation have been observed, which became more pronounced after the advent of IVF. Today, there are several protocols using different products from existing manufacturers and we the practitioners must choose between them.

The introduction of recombinant technology in this field and the utilization of recombinant FSH was a tremendous advance mainly because of some concerns about the possible hazards and potential risks of urinary gonadotrophin (Seeger *et al*., 2005). In addition, Daya (2002) demonstrated that recombinant FSH produced higher pregnancy rates per cycle with a lower amount of gonadotrophin than urinary FSH when follitropin α was used in IVF. This evidence is the best available in terms of quality and external validity (systematic review).

As discussed by Wikland *et al*. (2006), there is another point: recently the inaccurate in-vivo bioassay (Steelman and Pohley, 1953) was replaced by the more accurate method of size exclusion-high performance liquid chromatography. The main difference between these methods is that the amount of recombinant FSH per ampoule is less variable (batch-to-batch consistency) in the latter method (1.6%) compared with the former (12%) (Bassett and Driebergen, 2005).

Some investigators compared the two recombinant preparations, filled-by-bioassay (FbB) and filled-by-mass (FbM). They demonstrated that cycles stimulated with recombinant FSH (FbM) were more efficient with a significant shorter period of ovarian stimulation, lower amount of FSH, more oocytes retrieved and a better embryo quality (Abuzeid *et al*., 2001; Hugues *et al*., 2003; Balasch *et al*., 2004; Yeko *et al*., 2004). However, are these results the perfect evidence?

The main problem of these studies is the same problem for almost all questions regarding human reproduction: what is the best outcome for the patient? Moreover, assuming that the best outcome is a single healthy baby, what is the necessary sample size? The paper from Balasch *et al*. (2004) showed a non-significant difference in terms of clinical pregnancy (44% versus 35%) comparing both recombinant preparations (FbM and FbB, respectively). Calculating a sample size with those numbers and assuming a $P = 0.80$, we reach a calculated sample size of 461 patients in each group.

As discussed earlier, the perfect evidence sometimes does not exist and so we have to choose from the best available evidence. Currently, we do not have a properly randomized clinical trial with a sufficient sample size to compare both kinds of recombinant FSH. Nevertheless, the whole body of evidence currently available indicates that in terms of safety, accuracy and consistency, recombinant FSH FbM is presently the best alternative.

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