

Getting the Most out of Your Gonadotropin Dollar

**Kaylen Silverberg, M.D.
Medical Director
Texas Fertility Center
Austin, TX**

Infertility is estimated to affect at least 2.1 million couples in the United States and is all-too-often associated with impaired psycho-social well-being. Although continued improvements in assisted reproduction techniques (ARTs) such as in vitro fertilization (IVF) and controlled ovarian hyperstimulation (COH) have enabled many previously infertile couples to successfully conceive, the costs associated with such treatments remain high. To further complicate matters, although 15 states have mandated insurance companies to cover at least some forms of infertility treatment, the financial burden for most therapies is usually borne by the couple themselves. It is therefore of paramount importance to identify measures that could reduce the overall cost of infertility treatment.

While to the outside observer it may appear that the issue of cost-containment in infertility therapy should be an easy subject to assess and answer, for a variety of reasons, that is, unfortunately, not the case. Infertility patients represent a very diverse population. They vary by age, ovulatory status, the presence or absence – and even severity - of male factor, as well as the presence or absence of endometriosis, among many other factors. Unfortunately, many studies designed to look at various forms of fertility therapies fail to study isolated groups of patients.

Medications typically represent 30-40% of the cost of an IVF or COH cycle, with gonadotropins comprising the vast majority of this expense. It is therefore logical to assume that lowering the total gonadotropin bill will lower the overall cost of the ART cycle. However, before one simply chooses the least expensive gonadotropin, there are a variety of issues that must be considered.

For example, if one attempts to identify the optimal gonadotropin for use in ART, the results depend greatly on the specific population studied. Patients over 40 with severe male factor consistently experience low success rates. Therefore, in order to see a difference between two different gonadotropins, one would need to study a very large population of these patients. If too few patients are studied (i.e. the study has “insufficient statistical power”) then one will not be able to observe a difference between the two products even if a difference truly exists—leading to the erroneous conclusion that the two products are the same. These differences in patient populations are uniformly recognized, and while many ART studies include these differences during the planning stages, many still do not. This partially explains why such controversy persists regarding the “best” gonadotropin for ART. Some studies clearly demonstrate the superiority of

product A, whereas others favor product B or C. While it is possible that there is no “best” gonadotropin for ART, it is also possible that studies that have inappropriately lumped different populations of patients together have impaired our ability to distinguish between the different gonadotropins.

Unlike ten years ago, today’s practitioner has a variety of gonadotropins available for use in an ART cycle. While all have been associated with respectable pregnancy rates, there are significant differences among them. Some are isolated from human urine, while others synthesize the human FSH molecule using recombinant DNA technology - a process which results in enhanced purity and consistency. Some contain only follicle stimulating hormone (FSH), while others also contain luteinizing hormone (LH). Some can be injected subcutaneously, while others must be injected intramuscularly. While the specific gonadotropin used should certainly be selected by the physician who knows the intricacies of your medical condition, there are several issues that you may wish to consider.

When considering the issue of cost, it is of paramount importance to understand the difference between cost and cost-effectiveness. Whereas cost takes into account only the price of the medication, cost-effectiveness also considers the clinical effectiveness of the medication. For example, consider two hypothetical gonadotropins, Drug A and Drug B. Assume that Drug B costs twice as much as Drug A. Assume also that Drug B is more potent, so that fewer vials or ampules are required in order to achieve follicular maturity. In addition, assume that Drug B also happens to be more clinically effective than Drug A, producing a higher pregnancy rate per stimulation cycle. Therefore, even though Drug B is significantly more expensive per vial or ampule, overall it is more **cost-effective** than Drug A.

Over the years, thousands of scientific papers have been written evaluating the different gonadotropin preparations and comparing them to each other. Unfortunately, due to many of the reasons listed above, these studies have often yielded conflicting conclusions. Due to the multiple steps involved in a typical IVF cycle – each of which has several potential variables – it would be extremely difficult to design a trial that would assess the cost-effectiveness of a particular gonadotropin. Nevertheless, this information is of vital importance to healthcare policy makers, insurers, medical professionals and patients alike.

Therefore, a recent series of computer-simulated cost effectiveness models were developed in order to evaluate recombinant FSH (r-FSH) and urinary FSH (u-FSH) products while reproducing the conditions that exist in a typical IVF cycle with intracytoplasmic sperm injection (ICSI). These studies utilize results from the largest, most well-designed scientific trials as well as data from national IVF databases. Results were validated by an international panel of practicing fertility specialists with experience in clinical trials, epidemiology and statistics.

A “virtual” population of infertility patients was passed through this computer model until they achieved an ongoing pregnancy or until they completed a total of 3 treatment cycles, whichever came first. In order to ensure statistical accuracy, a population of 100,000 patients was studied over 5000 different simulations (can you define what a simulation is?). The total number of ongoing pregnancies was 40,665 with r-FSH compared to 37,890 with u-FSH. When typical costs of the gonadotropin preparations were included in the model (\$58.52 for r-FSH and \$61.09 for u-FSH), the cost per successful pregnancy using r-FSH was \$40,688 compared to a cost per successful pregnancy using u-FSH of \$47,096. Even when lower costs of \$49, \$45, and even \$40 were used for the u-FSH product, the mean costs per successful pregnancy of \$45,000, \$44,400, and \$43,500 were still significantly greater than the cost of the successful r-FSH pregnancy. Therefore, the authors concluded that, despite the higher cost of the recombinant FSH, its enhanced clinical efficacy made it the more cost effective choice.

In summary, the issue of getting the most out of your gonadotropin dollar is very complex indeed. Individual studies suggest conflicting results regarding product efficacy, and drug costs vary widely. Mathematical cost-effectiveness modeling overcomes the statistical limitations of small studies, while factoring in both drug cost and product efficacy, allowing one to choose the optimal gonadotropin based on cost-effectiveness.