Bye-bye urinary gonadotrophins?

Recombinant FSH: A real progress in ovulation induction and IVF?*

Norbert Gleicher1,2,3,4, Mary Vietzke2 and Andrea Vidali1

1The Center for Human Reproduction, New York, New York, 2The Center for Human Reproduction, Chicago, Illinois and 3The Foundation for Reproductive Medicine, Chicago, Illinois, USA

4To whom correspondence should be addressed at: Center for Human Reproduction, 60 East Delaware Place, Suite 1400, Chicago, Illinois 60611, USA. E-mail: CHRJournal@aol.com

Whether recombinant gonadotrophin products do, indeed, represent progress for routine ovulation induction and IVF cycles, in comparison with urinary products, has remained controversial. Here we review published data with regard to respective risks, outcomes and cost for both medication options. Safety considerations favour recombinant products, while overall outcome and cost considerations favour urinary gonadotrophins. Outcome, however, appears to differ, based on age and ovarian function, with younger patients benefiting from the FSH/LH combination offered by urinary products, while older women and young women with ovarian resistance, apparently benefiting from pure FSH stimulation. Young women with poor ovarian reserve may be best stimulated with a pure FSH/antagonist protocol. We conclude that under current pricing structures in the United States, recombinant gonadotrophins do not represent a major progress for the treatments of ovulation induction and IVF. They, however, allow for an improved selectivity of stimulation protocols. The creation of recombinant FSH/LH products and cost adjustments for recombinant products, may affect these conclusions in favour of recombinant products.

Key words: gonadotrophins/infertility/IVF/ovulation induction

Introduction

The last decade of the 20th century witnessed a potential milestone in the treatment of infertility as previously urine-derived gonadotrophins were increasingly replaced by gonadotrophins produced through recombinant technologies. These newer gonadotrophins are, however, considerably more expensive, especially since urinary gonadotrophins, in principle, have come off patent protection and can now be offered under generic pricing structures.

More costly pricing, however, does not necessarily indicate increased treatment costs. If more expensive medications improve treatment cycle outcomes, treatment cost per established pregnancy may, indeed, be unaffected or even reduced.

Cost considerations alone should, of course, not determine which of the gonadotrophin products are to be used in preference. The principal determining factor in any medical decision-making process is safety. Every medical activity has first and foremost to attempt to minimize potential risks and to establish a risk/benefit ratio, which then leads to a final determination whether a treatment should be considered at all.

Only at that point should cost become a consideration and a cost/benefit ratio be determined. Treatment decisions are thus the consequence of sequential risk/benefit and cost/benefit evaluations, and to a degree, always represent compromises.

Even though recombinant gonadotrophins have been widely embraced, only limited formal analyses on their performance have been reported in comparison with older urinary-derived products. Whether they represent real progress in ovulation induction and/or IVF is, therefore, at this point undetermined and will be the subject of this review.

Historical developments

The first hMG was approved in the United States in 1970, for follicular development in anovulatory and oligovulatory women (Nichols et al., 2001). It remained the mainstay of fertility treatment for almost 20 years.

This product was obtained from the urine of postmenopausal women. Postmenopausal urine contains both FSH and LH in high concentrations. hMG, indeed, consists of approximately one half FSH and LH, though intermixed with a relatively high concentration of co-puriﬁed urinary proteins. Until recently, hMG was administered exclusively by i.m. injection. Its clinical efﬁcacy in achieving ovulation, or so-called ‘controlled ovarian hyperstimulation’, has been established beyond any reasonable doubt (Lunenfeld et al., 1962; Tsapoulis et al., 1978; Goldfarb et al., 1982) and pregnancy rates of ~11.7% per

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Urinary versus recombinant gonadotrophins

Is there a difference in safety?

Whether recombinant gonadotrophins, indeed, offer an improvement in safety margins over the older urinary products is one of the most crucial questions in this analysis.

Many scientists strongly argued that: (i) a pure (i.e. recombinant) product was in principle preferable to an impure (i.e. urinary) product; (ii) human (i.e. urinary) products carried a risk of infection by slow-viruses, raising concerns; (iii) human products, since impure, carried a risk of immunogenicity and (iv) human products had repeatedly been demonstrated to be uneven in biological potency.

These four arguments, all basically favouring medical modernity over older-line products, and all representing basic common sense, carried considerable impact and greatly contributed to the dramatic marketing success of recombinant gonadotrophins.

Let us examine these arguments, however, one by one: indeed, it is difficult to argue with the basic premise that purity is preferable to impurity. Yet, impurity affects safety only if it can be demonstrated that any of the potential contaminants adversely affect either the patient’s health or the treatment’s outcome. Since outcome comparisons will be discussed below, let us now concentrate on the aspects of safety.

In over 30 years of clinical use of urinary gonadotrophins, not a single case of infectious contamination has been reported. Even cases of slow viruses should, in such a time span, have clinically become apparent (Balen, 2002).

In contrast, the risk of immunogenicity appears more realistic: Biffoni et al., representatives of one of the major pharmaceutical companies in the field, report that during a conventional IVF cycle, only approximately 0.2 mg of 15 mg or more, of protein which is administered in the form of urinary gonadotrophins, is either FSH or LH. The rest is contamination by-product with, at least theoretically, immunogenic potential (Biffoni et al., 1998).

Mostly case reports in the literature do support such a risk (Harika et al., 1994; Odink et al., 1995; Redfearn et al., 1995; Albano et al., 1996). Moreover, every practitioner in the field has encountered patients with significant local, allergic reactions, especially with i.m. administration. A recent safety study, supported by one of the manufacturers of an hMG product with Food and Drug Administration approval for both, i.m. and s.c. administration, demonstrated actually significantly increased injection site oedema and/or reaction with s.c. administration over i.m. administration of the same, or a competitor’s product (Ferring Pharmaceuticals Inc. 2002).

Allergic reactions are of concern, since they can activate immune processes that may be hostile to implantation and increase miscarriage risks (Gleicher, 2002).

Biffoni et al. (Biffoni et al., 1998) demonstrated that preparations from different manufacturers have different in vitro immunological effects, which may reflect a different profile of contaminants. It even appears doubtful whether products from the same manufacturer will maintain their immunological profile. No such study has ever been performed.

Nobody has been able to link the occurrence of antiphospholipid antibodies (APAs) with gonadotrophin therapy (Franklin et al., 1998). However, allergic reactions can be associated with significant shifts in Th1/Th2 activities, which can include APA-responses, and which, of course, have been closely linked to an increased risk of infertility and pregnancy wastage (Gleicher, 2002).

The conclusion has, therefore, to be reached that recombinant medications, indeed, are less immunogenetic than the older urinary-derived medication and, at least from this point of view, are preferable.

Uneven biological potency also carries significant risk, since controlled ovarian stimulation can become less predictable. Practitioners in the field have long complained about varying bio-potency of different batches of urinary gonadotrophin products. Such reports have, however, remained largely anecdotal. Moreover, while recombinant products may be easier to standardize, variations in bio-potency can also occur if this production technique is applied. There is currently no convincing evidence in the literature to favour recombinant over urinary products, because of prospective ovarian stimulation risks, though there have been suggestions in the literature that rFSH may decrease ovarian hyperstimulation risks (Aboulghar et al., 1998).

Finally, one also has to consider the biological risk exclusive to recombinant products: such, FSH is produced by transfixing a genomic clone (which causes the coding sequences for the FSH α- and β-subunits) into Chinese hamster ovary cells, which then synthesize the FSH protein (Prevost, 1998). As an animal cell product, this creates the theoretical risk of introducing animal viruses into humans. Like the previously
noted concern about the introduction of slow viruses through urinary products, pharmaceutical filtering and purification techniques make this, however, only an issue of theoretical concern. In summary in regards to safety, there was a slight advantage in recombinant products.

Is there a difference in outcome?

Very limited comparative data have been published on the use of urinary versus recombinant gonadotrophins for ovulation induction purposes only (Yarali et al., 1999).

In contrast, the literature offers a large cohort of studies on the impact of different gonadotrophin preparations on IVF. Unfortunately, however, the opinions are not consistent.

Theoretical background

It has been suggested that excessive LH levels can adversely affect reproductive outcome. Specifically, high LH levels may affect fertilization success (Stanger and Yovich, 1985), implantation rates and, subsequently, pregnancy rates, as well as early embryonic development and increase the miscarriage risk (Homburg et al., 1988; Regan et al., 1990; Chappell and Howles, 1991). Consequently, it was argued that the removal of LH from gonadotrophin preparations would be beneficial for overall pregnancy outcome, by reducing LH exposure of patients, often already suffering from LH excess.

Recent studies have, however, raised significant questions about this concept. For example, Barnes et al. (2002), in the study of a patient with isolated FSH deficiency and multicystic ovaries, found no clinical or laboratory consequences from the patient’s LH excess. Nichols et al. (2001), in fact, recently concluded that despite differences in treatment protocols a preponderance of clinical trial data suggest that the presence of LH is not detrimental, when used in women with an otherwise good prognosis. They buttressed their argument with an extensive reference list (Scoccia et al., 1987; Bentick et al., 1988; Lavy et al., 1988; Edelstein et al., 1990; Imthurn et al., 1996; Check and Fine, 1997).

What exact role LH plays in early folliculogenesis has remained controversial. Recent reports have cast doubt on at least some aspects of the classical two cell, two gonadotrophin theory which contends that both, FSH and LH, are required for folliculogenesis in the human experience (Fevold, 1941). For example, FSH has been reported as not necessary for the development of small, healthy antral follicles readily responsive to FSH (Barnes et al., 2002).

According to the two cell, two gonadotrophin theory, only low dosages of LH are required to achieve good follicular growth and oocyte maturation, with (long) luteal phase GnRH suppression. Yet, in some patients, such dosages may not be enough (Barnes et al., 2002), either due to low serum concentrations (Noci et al., 1998) or low bioactivity of LH (Schoor et al., 1999). Such patients may benefit from LH-containing gonadotrophin products (Söderström-Anttila et al., 1996; Westergaard et al., 1996).

Westergaard et al. (1996) also suggested that profoundly suppressed LH levels, as may be seen in ovarian stimulation cycles with pure FSH stimulation (after GnRH agonist down-regulation), may lead to a higher prevalence of early pregnancy loss and, consequently, lower take-home baby rates. Midfollicular LH levels <0.5 IU/l appeared to indicate risk.

Analysing all of these data in unison, it appears increasingly likely that maximal reproductive success on the physiological level will be achieved within a ‘normal’ therapeutic range of LH. Both too low and too high LH levels appear detrimental before, as well as after implantation. Since patients outside this ‘normal’ therapeutic LH range cannot be reliably identified, and since a majority of studies at least concur that low (though not too low) LH levels are not detrimental to reproductive outcome, currently available data would appear to support a low level of LH substitution (at least in GnRH agonist down-regulated cycles).

In summary, from a theoretical viewpoint urinary gonadotrophins appear to be at an advantage.

Ovarian stimulation without IVF

Only very limited comparative outcome data for the utilization of urinary and recombinant gonadotrophins are available. Yarali et al. (1999) in a prospectively randomized study reported similar outcomes for both treatment options, though noted that their outcome contradicted a number of other studies, which had suggested a mild outcome advantage for rFSH. In contrast, in a retroactively analysed cohort study involving large cycle numbers, we reported evidence that in unselected patients, mostly undergoing IUI cycles, there appeared no benefit to purer FSH preparations and, in fact, there may have been a detriment (Gleicher and Karande, 2000).

Here, study size is of obvious importance; since expected pregnancy rates per cycle are low at ~12–15% (Lunenfeld and Lunenfeld, 1997; Gleicher and Karande, 2000), large patient numbers are required to show statistically significant outcome differences; and, even statistically significant pregnancy rate differences may appear clinically as irrelevant!

The literature, therefore, does not allow for a preferential judgement of hMG over highly purified FSH for ovulation induction cycles at this point. Moreover, since outcome results are so similar, it is likely that any statistically valid outcome difference, potentially detectable with larger population studies, will demonstrate only minor differences of no or only very limited clinical advantage for either product.

In summary there was no advantage for either.

Ovarian stimulation for IVF

An abundance of studies addressed the question whether highly purified urinary FSH products or rFSH do or do not improve IVF outcome. As is usually the case, these studies vary in format, study size, IVF protocols, patient populations and pharmaceutical products used. They, of course, also differ in basic pregnancy rates achieved through the IVF process and in patient selection (i.e. rejection from entry into an IVF cycle).

As is widely recognized, IVF outcomes can, therefore, not be compared between IVF programmes (American Society for Reproductive Medicine, 1999). Yet, this is exactly what is
done, indirectly, when meta analyses on the subject are reported.

A first such meta analysis was reported in 1995 by Daya et al. (1995) and has, since, become the principal reference for the substitution of hMG by purified and/or rFSH. In this study, for the first time, a claim was made that the exclusive stimulation with highly purified or rFSH products resulted in significantly higher IVF pregnancy rates than stimulation by hMG. Paradoxically, a large majority of studies forming the material for the meta analyses were, themselves and independently, unable to support such a claim. Daya and Gunby (1999) followed up their initial study with yet another meta analysis in 1999, which offered additional evidence for the benefit of rFSH over urinary-derived, purified FSH products.

Considering the conceptual difficulties with meta analyses in addressing outcome questions in this arena, it will not come as a surprise that in a meta analysis by Agarwal et al. (Agarwal et al., 2000), where studies evaluated in the earlier meta analyses were reanalysed, very different conclusions were reached. This meta analysis, in fact, concluded that in ovarian stimulations, following down-regulation with a GnRH agonist, stimulation by either FSH or hMG was equally effective.

After initial completion of this manuscript, Daya (2002) reported yet another update on his meta analyses, comparing rFSH with urine-derived FSH. This paper was based on a presentation at a consensus meeting on optimizing ovulation induction in assisted reproductive technologies in Santa Monica, CA, in August 2000 and well documents the above-noted apprehensions about the use of meta analyses in this arena.

Daya, once again, concludes that rFSH resulted in higher pregnancy rates than the urinary product; however, this conclusion applied only to follitropin-alpha (and not to follitropin-beta); i.e. the pharmaceutical product produced by transfecting Chinese hamster ovary cells with α-subunit genes. Moreover, the magnitude of the improvement in pregnancy rate was extremely small, as acknowledged by the author. This would mean that for every 19 women undergoing IVF, one additional clinical pregnancy could be expected (Daya, 2002).

Daya’s new paper included six studies, which had not been included in his prior publications (Daya et al., 1995; Daya and Gunby, 1999). These studies were published between 1997 and 1999 and, therefore, reflected clinical experiences preceding this range of dates.

Blumenfeld (2001) recently pointed out yet another difficulty in assessing IVF outcomes that were accumulated over long time periods: IVF success rates, of course, improve year-by-year. Any comparison of earlier with later outcomes, even within one programme, will, therefore, introduce unacceptable biases. It is, therefore, difficult to understand how IVF outcomes of different time periods can be part of a meta analysis, without consideration of this fact.

Since women with ‘normal’ ovarian function usually undergo ovarian stimulation after down-regulation with GnRH agonists, and only women with ‘poor’ ovarian function undergo other forms of stimulation, pure FSH stimulation may have marginal benefits in women with abnormal ovarian function. Though, even this observation awaits further confirmations, since one cannot rule out that the observed benefit comes from confounding factors, such as short or no GnRH agonist administration.

These conclusions are well supported by a series of recently published studies, which have appeared following the most recent meta analyses: Ng et al. (2001) reported no significant differences in oocyte and embryo quality, as well as pregnancy rates, with trends favouring the use of hMG. Small study numbers (n = 20 in each group), of course, do not exclude the possibility of a Type-2 error (i.e. falsely accepting the null hypothesis).

Westergaard et al. (2001) in an IVF study like Ng’s, with the use of ICSI, in fact, concluded that hMG gave statistically superior pregnancy rates, while oocyte and embryo quality was similar between FSH and hMG stimulation. These authors also point out the difference in outcome between s.c. and intranasal GnRH agonist administration, further advancing the argument in favour of multiple co-variants affecting IVF outcome.

De Placido et al. (De Placido et al., 2001) addressed the question in a rather ingenious protocol. They started two randomized groups of poor responding women on 150 IU rFSH twice daily, but substituted only in one after day 8 the evening dose with 150 IU hMG, while the other group was increased to 375 IU rFSH daily overall. The hMG-treated group had significantly more oocytes, though the higher pregnancy rate (50%) did not reach significance in comparison with the pure FSH group (25%). A Type-2 error, however, cannot be ruled out in view of small sample sizes.

Women with poor ovarian response may, indeed, offer a very reflective view into abnormal ovarian function, which, in addition, may exaggerate conditions observed in a normally functioning ovary. In this sense, the observations reported by De Placido et al. may have additional significance (De Placido et al., 2001).

Such a conclusion is also supported by some preliminary data accumulated at our centres, which will be reported elsewhere in detail (N.Gleicher, unpublished data). As a summary, we can state, however, that poor responders treated with either early recombinant FSH or FSH/LH, in combination with either a GnRH agonist microdose protocol or a GnRH antagonist, did better with an antagonist protocol. Yet, a more detailed analysis reveals some subtle and surprising differences in outcome. Specifically, it appears that the young (≤34 years) and the very old (>41 years) behave differently from women in the middle-aged group. The former clearly appear to benefit from pure FSH stimulation, with the young apparently gaining additional benefit from an antagonist, while the older females do clearly better with a microdose agonist. In contrast, the median age group of patients with ovarian resistance seems to do better with FSH/LH combinations, whether with agonist or antagonist support.

Such age-specific findings are interesting, because they suggest that the young ovary with ovarian resistance, in contrast to the normal young ovary, is indeed better off with rFSH stimulation and, thus, closely mimics the physiologically-aged ovary above the age of 41. Yet, those two ovaries also appear to differ because the young resistant ovary does best with antagonist support, while the aged resistant
ovary requires microdose agonist support. In view of such surprising age-specific outcomes, we are currently re-evaluating historical IVF data, stratified for age and ovarian function, in anticipation of detecting further age- and ovarian function-specific benefits of different ovarian stimulation protocols.

The largest study size amongst any recently reported study came from Strehler et al. (2001). In 282 hMG and 296 rFSH cycles, the authors reported a statistically larger number of oocytes retrieved with rFSH and statistically higher medication use with rFSH, while pregnancy rates did not differ.

Gordon et al. (2001) in an attempt to define the need of exogenous LH-dosage on IVF outcome, randomized patients to either rFSH or an increasing dosage of LH. Statistically, there were no differences noted between the groups, though a significantly improving trend in the implantation rates was noted with increasing LH dosages. Small group sizes, once again, raised the spectre of a Type-2 statistical error. In summary overall IVF data suggest a slight advantage for urinary products.

Cost analysis
Since the preceding risk-benefit and outcome analyses do not reveal an overwhelming advantage for either urinary or recombinant products, the cost analysis for both treatment options assumes added importance. Yet, the available data are extremely limited and this fact should not surprise.

Cost analyses in infertility therapy are extremely complex, since they involve not only treatment and medication costs, but also need to consider the subsequent expense for the outcomes achieved. A singleton pregnancy that leads to uneventful delivery, of course, will ensure lower costs than a multiple pregnancy that ends up in a very premature delivery. Consequently, the degree of control over multiple births represents not only an important quality of care issue, but will greatly affect any sensible cost analysis and, therefore, affect treatment choices. It is for that reason, for example, that we suggested that most ovulation induction cycles should be abandoned and replaced by IVF cycles with a limited number of embryos being transferred (Gleicher et al., 2000).

A high prevalence of ovarian hyperstimulation syndrome will generate cost, which a low incidence will avoid. The same applies to high versus low cycle cancellation rates, other complications and, finally, pregnancy rates. What all of this demonstrates is the subjectivity of all cost data and the futility of attempts to establish objective treatment costs.

It is, therefore, not surprising that only limited cost effectiveness data are available. Moreover, all the limited published cost effectiveness data are suspect since they are not based on actual experiences (which, as noted above, would also have to be considered questionable in regards to their universal applicability), but rely on modelling. Specifically, Balasch and Barri (Balasch and Barri, 2001), in an attempt to compare the cost effectiveness of urinary and rFSH in Spain, concluded that rFSH represents the more cost effective option. In so doing, they established so-called ‘background concepts’ and applied similar review criteria as expressed in this paper. They, in addition, performed a Markov model analysis, based on their interpretation of the literature that rFSH results in better clinical pregnancy rates than urinary FSH products.

As we already noted, we cannot agree with such an interpretation of the literature. Therefore, we have to consider the authors’ conclusions as suspect.

Silverberg et al. (2002) (inclusive of co-authors who are representatives of a major pharmaceutical manufacturer), also utilizing theoretical clinical decision analysis techniques, following the Markov model, came to similar conclusions as Balasch and Barri, and stated that rFSH is more cost effective per ongoing pregnancy, than a urinary FSH stimulation. However, these authors, as well, reached this opinion based on a concomitant conclusion that rFSH was also the clinically superior product in terms of pregnancy outcome. Furthermore, they concluded that “the economic effectiveness of a drug depends less on its acquisition costs and rather more on the clinical outcomes associated with its use.”

While this statement may, under certain circumstances, be correct, our analysis of comparative outcome data for urinary and recombinant gonadotrophins does not allow us to concur that this conclusion applies to the current circumstances faced by physicians who have to choose between urinary and rFSH. In fact, our interpretation of the literature, which suggests very similar outcomes for both of these treatment options, leads to exactly the opposite conclusions: where outcomes are similar, acquisition costs for the respective medications appear especially relevant.

Barlow (2001), recently published an Editorial in conjunction with the publication of two cost effectiveness studies in his journal. It clearly summarizes the challenges with publications of such studies. Besides complexities of analytical methodologies, he also addressed the question whether pharmaceutical companies, with considerable economic self interest, should be involved in such modelling studies (both studies in Human Reproduction had such involvement) and openly revealed differing opinions by the journal’s reviewers.

Indeed, both published studies, one by Sykes et al. (2001) and the other by Daya et al. (2001) suggested that rFSH represented the most cost effective medication for ovarian stimulation during IVF cycles. Yet, the underlying assumptions used for Markov modelling, once again, were based on, in our opinion, erroneous interpretations of the published literature, assuming an outcome benefit for rFSH.

The literature appears almost unanimous in that rFSH cycles require slightly lower overall stimulation dosages than urinary products. This could, of course, represent significant savings. Unfortunately, the literature currently does not allow an assessment of the potential degree of such savings since the stimulation protocols applied and resultant outcomes vary, to a very significant degree.

Acquisition costs of medication
As, in our opinion, neither risks nor outcomes overwhelmingly favour either urinary or recombinant gonadotrophins, acquisition costs for these medications assume prime importance. Table I summarizes approximate purchasing costs per 75IU of gonadotrophins in the USA and in some other markets. As will
Table 1. Selective acquisition costs of gonadotrophin products in selected markets (per 75 IU)\(^a\)

<table>
<thead>
<tr>
<th>Market</th>
<th>hMG</th>
<th>rFSH</th>
</tr>
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<tbody>
<tr>
<td>United States</td>
<td>44.99–49.93</td>
<td>57.99–63.92</td>
</tr>
<tr>
<td>Canada (Canadian dollars)</td>
<td>48.74</td>
<td>73.94</td>
</tr>
<tr>
<td>UK (US dollars)</td>
<td>18.00</td>
<td>49.95</td>
</tr>
<tr>
<td>France (US dollars)</td>
<td>10.00–15.00</td>
<td>40.00</td>
</tr>
<tr>
<td>Pakistan (US dollars)</td>
<td>33.51</td>
<td>140.16 (100 IU)</td>
</tr>
<tr>
<td>Italy (US dollars)</td>
<td>12.50–20.00</td>
<td>37.00</td>
</tr>
</tbody>
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\(^a\)Obtained from internet advertisements

be very apparent, urinary gonadotrophins and, especially hMG, offer a very significant cost advantage.

Therefore, we have to conclude that in terms of overall cost-effectiveness, the urinary products carry the day. However, this conclusion is subject to change if the decrease in needed medication dosage with the use of rFSH can be confirmed, quantified and would allow the conclusion that it can compensate for higher rFSH unit costs.

In summary, there was an advantage to urinary products.

Conclusions

Recombinant gonadotrophins represent a very obvious technical progress in comparison with the older urinary gonadotrophins. This appears most clearly in their relative ease of administration and in their lack of contaminants, which in urinary products are prevalent and can cause immunological reactions.

There is, however, no convincing evidence that rFSH improves clinical outcome in either standard ovulation induction or with IVF. In fact, the opposite may be true and LH-containing gonadotrophins may have an outcome advantage, especially in younger women with normal ovarian function, who undergo down-regulation with GnRH-agonists.

Since outcome affects cost to a large degree, the lower acquisition costs of urinary products represent a very significant factor in choosing a preferred medication.

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