Introduction

Infertility is a common problem worldwide, affecting approximately up to 15% couples, with varying rates in different parts of the world.\(^1\) Worldwide, the incidence of infertility is on the rise. Factors such as delayed age of marriage, late start of family, sedentary lifestyle resulting in obesity, malnutrition, stress, smoking, and drug or alcohol addiction are some of the factors contributing toward the rising infertility and adverse impact on the fertility.\(^1\) A study showed 12.6% prevalence of primary infertility among young women.\(^2\) The rates of infertility are higher in urban women, possibly due to lifestyle (stress and dietary habits) and late marriage.\(^3\) Approximately 1% women develop premature ovarian failure before the fourth decade of life, mostly due to idiopathic reasons. Ovulation induction and fertility can be achieved in a significant number of these women with a multispecialty management approach.\(^4\) Gonadotropin therapy is an important component of infertility management. Since the introduction of gonadotropins, there have been significant advances in its developments, especially during the past two to three decades. Currently, gonadotropins are widely used worldwide for ovulation induction and controlled ovarian stimulation, especially in

Abstract

Globally, about 10%–15% couples are affected by infertility, with major role being played by the couple’s lifestyle. Several gonadotropin preparations (urinary, purified urinary, recombinant, and biosimilars) are available for use. Purified urinary formulations offer numerous advantages over their predecessor, including lesser injection dose required, ability to be administered subcutaneously, less batch-to-batch variability, better efficacy, ability to individualize protocols as per patient’s need, better control of developing follicles, less risk of multiple pregnancies, and hyperstimulation. Published results of Cochrane reviews and meta-analysis show no difference in efficacy or safety between urinary and recombinant gonadotropins. In the absence of any significant difference, cost plays an important role in deciding choice of gonadotropins. In this article, we have reviewed the results of comparative clinical trials, Cochrane analysis, and meta-analysis to derive consensus statements regarding efficacy, safety, and cost implications of urinary versus recombinant gonadotropin preparations.

Keywords: Ovulation, recombinant, urinary gonadotropins
women undergoing treatment with assisted reproductive technology (ART). The use of gonadotropins for multiple follicular development has significantly improved the outcomes rates of in vitro fertilization (IVF) through controlled ovarian stimulation.[9]

**History and evolution of gonadotropin preparations**

In 1910, experimental studies by Crowe et al. suggested the role of pituitary in regulating gonads.[6] In 1927, a substance from blood and urine of pregnant women was shown to be capable of stimulating gonads in female mice, resulting in maturation of follicles and luteinization.[7] Later in 1930, blood and urine of postmenopausal women was shown to contain gonadotropins.[8] The first commercial human chorionic gonadotropin (hCG) preparation became available in 1931. However, it was observed that hCG alone in the absence of follicle-stimulating hormone (FSH) has no effect in the follicular phase. Gonadotropins derived from the blood of pregnant mares and from cadaveric pituitary glands showed an ovarian response and were used in the western world till the early 1960s. Withdrawal of human pituitary gonadotropins was a result of therapy-associated limitations such as development of neutralizing antibodies against the preparation and cases of dementia and deaths due to Creutzfeldt–Jakob disease.[5,9] This withdrawal prompted the process of extraction and purification of gonadotropins from other human sources, i.e., urine, leading to the development of hCG (from urine of pregnant women) and human menopausal gonadotropin (hMG).[5,10]

During the early 1970s, clinical practitioners felt the need for different treatment regimens and dosages of FSH and luteinizing hormone (LH) for individual patients, which required urinary gonadotropin formulations to be almost free from LH.[9] This resulted in the development of purified urinary FSH (uFSH) preparations, with negligible LH activity. Crude extraction techniques, high volumes of urine required for sourcing gonadotropins, and presence of urinary impurities were the major disadvantages of the older urinary preparations.[11] Purity of urinary gonadotropins was further improved with technological advances including nanofiltration techniques, which resulted in the development of highly purified (HP) hormones.[10,12] The advantages of these preparations include lesser injection dose requirements, ability to be administered subcutaneously, reduction in batch-to-batch variability, improved efficiency, ease of the development of individualized protocols based on the patient’s need, with better control of developing follicles, less risk of multiple pregnancies, and hyperstimulation.[9]

With the use of recombinant DNA technology,[13] more recently, recombinant FSH (rFSH) has been produced without the need for extraction from postmenopausal urine.[13,14] This recombinant human FSH (rhFSH) is similar to uFSH, with minor structural changes in the carbohydrate side chains and more basic isoformes.[15]

Major developments in gonadotropins during the past four decades are summarized in Table 1.[15]

Currently used gonadotropins are derived either from the urinary source or using recombinant technology.[16] List of urinary and recombinant preparations is given in Table 2. FSH-containing gonadotropin preparations are hMG (which contains both FSH and LH), uFSH, HP uFSH, and rFSH [Figure 1].[10]

Given the availability of purified, HP urinary, and recombinant gonadotropin preparations, clinicians are faced with the following questions:

1. Is rFSH really a cost-effective option over urinary gonadotropins?
2. Is there any clinical difference between urinary and rFSH in terms of safety and efficacy?
3. What factors should be considered while choosing a gonadotropin preparation?

The objective of this paper is to compare recombinant gonadotropins (rFSH) with urinary gonadotropins

---

**Table 1: Developments in gonadotropins in the past four decades**

| Year | Milestone in gonadotropin development |
|------|--------------------------------------|
| 1980 | FSH-only products                     |
| 1993 | Highly purified urinary FSH           |
| 1995 | Rec-hFSH                             |
| 2000 | Rec-hLH                              |
| 2001 | Rec-hCG                              |
| 2004 | FbM rec-hFSH formulation             |
| 2010 | Long-acting FSH gonadotropin         |
| 2011 | Novel pen devices to deliver precise doses |

**Table 2: Urine derived and recombinant preparations**

| Urine derived preparation | Recombinant preparation |
|---------------------------|-------------------------|
| hMG                       | Rec-hFSH                |
| HP-hMG                    | Long-acting FSH         |
| HP-FSH                    | Rec-hLH                 |
| U-hHCG                    | Rec-hFSH + rec-hLH 2:1 |
|                           | Rec-hCG                 |

FSH=Follicle-stimulating hormone, LH=Luteinizing hormone, hCG=Human chorionic gonadotropin, FbM=Filled-by-mass, Rec-hFSH=Recombinant human FSH, Rec-hCG=Recombinant hCG, Rec-hLH=Recombinant human LH
(i.e., hMG, purified FSH, and FSH-HP) vis-à-vis safety and efficacy for ovarian stimulation in women undergoing assisted reproductive therapy.

**Methodology**

Comprehensive literature search was performed in “PubMed” and “Cochrane” database to screen the articles related to evolution of gonadotropins from animal preparations to the recombination formulation and use of recombinant gonadotropins versus urinary gonadotropins (i.e., hMG, FSH-P, and FSH-HP) for ovarian stimulation in women undergoing assisted reproductive therapy and ovulation induction in polycystic ovarian syndrome (PCOS). Studies comparing urinary or HP urinary gonadotropin preparations with recombinant gonadotropins were considered for the review. The parameters of evaluation included efficacy, safety, quality of oocytes, cost-effectiveness, and route of administration. The consensus statements are prepared based on results of clinical studies and its applications in clinical practice.

**Efficacy and safety of urinary gonadotropins versus recombinant formulations**

Two Cochrane reviews[17,18] and two meta-analyses[19,20] comparing urinary with recombinant gonadotropins are considered in this review. van Wely et al.[17] analyzed results of all randomized controlled trials (RCTs) which reported comparative outcomes between rFSH and urinary gonadotropins (hMG, HP hMG, and purified or HP uFSH) in women undergoing IVF/intracytoplasmic sperm injection (ICSI) cycles. They included 42 clinical trials involving 9606 couples. Analysis of results of 11 clinical trials (n = 3197) revealed significantly lower live-birth rate after rFSH administration than hMG (odds ratio [OR] = 0.84, 95% confidence interval [CI] = 0.72–0.99). Similarly, analysis of five clinical trials (n = 1430) showed no significant difference in live-birth rate between rFSH versus FSH-P (OR = 1.26, 95% CI = 0.96–1.64) and rFSH versus FSH-HP (OR = 1.03, 95% CI = 0.86–1.22). Moreover, live births after fresh cycles and cumulative live-birth rate after fresh and frozen-thawed cycles were similar with rFSH and urinary gonadotropins. There was no significant difference in the ovarian hyperstimulation syndrome (OHSS) rate between rFSH and urinary gonadotropins (32 trials, n = 7740; OR = 1.18, 95% CI = 0.86–1.61). There were no differences between urinary and recombinant gonadotropins with respect to clinical pregnancy rates, multiple pregnancy rates (per woman and per pregnancy), and miscarriage rates.[17] Weiss et al.[18] compared outcomes of urinary and recombinant gonadotropins for ovulation induction in women with clomiphene citrate-resistant PCOS. A total of 14 randomized clinical trials involving a total of 1726 women were included in the analysis. Out of 14 clinical trials, ten compared live-birth rates per women with rFSH versus urinary gonadotropins. There was no difference in live birth (five trials; OR = 1.26, 95% CI = 0.80–1.99; live-birth rate with uFSH 16% vs. rFSH 13%–26%). The subgroup analysis of urinary gonadotropin (rFSH vs. HP-hMG or FSH-HP) did not show difference. Clinical pregnancy rate per women (eight trials; OR = 1.08, 95% CI = 0.83–1.39) was similar. Similarly, the subgroup analysis (rFSH vs. HP-hMG or FSH-HP) did not show difference. There was no difference in the multiple pregnancy rate or miscarriage rate overall as well as within the subgroups. There was also no difference in OHSS rates between urinary gonadotropins and rFSH or hMG/HP-hMG.[19]

A systematic review of 12 randomized trials and 3575 women compared hMG with rFSH in terms of clinical safety and efficacy in assisted reproduction. The analysis demonstrated significantly higher live-birth rate with hMG compared with rFSH (OR = 1.20, 95% CI = 1.01–1.42). There was no significant difference in the rates of OHSS (OR = 1.21, 95% CI = 0.78–1.86) between two groups. Clinical pregnancy rate was significantly better with hMG. In this analysis, clinical outcomes were better with hMG than rFSH without significant difference in the patient safety.[20]

A meta-analysis (2003) of 20 RCTs by Al-Inany et al.[19] comparing rFSH versus uFSH did not show a significant difference in the pregnancy rate per started cycle (OR = 1.07; 95% CI = 0.94–1.22). Similarly, pregnancy rate per started cycle was similar between rFSH versus hMG, FSH-P, and FSH-HP.[19]

**Advanced maternal age and efficacy of gonadotropins**

There is rising trend toward increased age at marriage for both, men and women, resulting in increase in infertility. Increased maternal age also poses a significant challenge to the infertility specialist due to poor-quality oocytes and inadequate response to controlled ovarian hyperstimulation, ultimately leading to poor ART outcomes. Purified uFSH has shown to be more effective in older women compared to rFSH with the long protocol. In a controlled prospective trial, patients were randomized to receive either rFSH (n = 121) or
Patients treated with uFSH required a significantly lesser amount of FSH (both total and FSH per oocyte) as compared to rFSH. Comparative pregnancy rate (19.2% vs. 17.3%) and implantation rate (10.4% vs. 8.6%) were not significantly different between uFSH and rFSH groups.\textsuperscript{[21]}

In retrospective analysis of 3178 Chinese infertility patients with IVF/ICSI treatment cycles, HP-FSH showed (n = 1932) similar live-birth rate when compared with rFSH (n = 1246). The patients in HP-FSH group were older (32 ± 4 vs. 30 ± 4, P < 0.01) compared to those in rFSH group. No significant difference was seen in the implantation rate (30.49% vs. 32.45%) as well as clinical pregnancy rate per cycle (41.61% vs. 41.97%).\textsuperscript{[22]}

A recent prospective, randomized study in Chinese women over 37 years undergoing treatment for IVF/ICSI cycles showed significantly better 2PN zygote rate (87.4% vs. 76.6%, P < 0.001), Grade 1 embryo rate (49.8% vs. 40.8%, P < 0.001), endometrial thickness on the day of hCG (11.8 vs. 11.2 mm, P = 0.006), and lesser number of nontransferable embryos (1.2% vs. 5.3%, P = 0.019) with uFSH as compared to rFSH. uFSH contains more acidic isoforms with a slower clearance, longer half-life, and better biological activity than rFSH.\textsuperscript{[23]}

### Summary

With improved extraction and purification procedures, the urinary preparations show comparable efficacy to recombinant formulations.\textsuperscript{[11]} Based on the available evidence, it can be concluded that there is no significant difference between recombinant and urinary gonadotropins, vis-a-vis safety, and efficacy. Urinary gonadotropins may in fact result in better outcomes in women with advanced maternal age (>35 years), as compared to the recombinant variety.

### Consensus statement

Available evidence from the published literature does not show significant difference between urinary and recombinant gonadotropins in terms of safety and efficacy.

### Quality of oocytes retrieved and quality of embryo transferred

Several trials\textsuperscript{[24-30]} have compared embryo and oocyte quality in patients receiving recombinant versus urinary formulations. Studies by Hedon et al.\textsuperscript{[24]} (comparing rFSH vs. uFSH in infertile women undergoing IVF and embryo transfer), Ng et al.\textsuperscript{[25]} (women undergoing ovarian stimulation for ICSI with either hMG or rFSH), and Strehler et al.\textsuperscript{[26]} (comparing rFSH and hMG in women undergoing IVF/ICSI) reported no significant difference in oocyte and embryo quality between urinary and recombinant gonadotropins.\textsuperscript{[24-26]}

Selman et al.\textsuperscript{[27]} compared HP uFSH versus rFSH in IVF/ICSI. Their results demonstrated a significantly higher Grade 1 embryo score in the uFSH group compared to rFSH whereas Balasch et al.\textsuperscript{[28]} showed a higher number of good quality zygotes and embryos in rFSH group compared with hMG in patients undergoing ICSI. Cheon et al.\textsuperscript{[29]} compared rFSH versus HP-FSH (uFSH) in women undergoing controlled ovarian hyperstimulation in IVF-ET and showed a higher number of good-quality oocytes in the rFSH group (P = 0.024), but there was no difference between two groups in the quality of transferred embryos. In another retrospective study, the quality of oocytes produced by HP uFSH was found to be better than those produced by rFSH.\textsuperscript{[30]}

### Role of luteinizing hormone in folliculogenesis

According to the two-cell–two-gonadotropin theory,\textsuperscript{[31]} FSH stimulates follicular development and both LH and FSH are required for estradiol synthesis: LH binds to receptors in the thecal layer to trigger androgen precursors to move from the theca to the granulosa cells, where, through the FSH-stimulated action of aromatase, they are converted to estrogen in humans. FSH and LH are involved in the synthesis of growth factors needed for the regulation of follicular maturation. LH also helps in maintaining function of granulosa cell during intermediate and late phases of follicle synthesis,\textsuperscript{[12]} support deselection of nondominant follicles, and play a role in regulation and integration of granulosa and theca cell functions during late preovulatory phase, oocyte maturation of the dominant follicle, and luteinization of the cumulus oophorus.\textsuperscript{[33]}

The growth of nondominant follicles is stopped by LH surge at mid-cycle. “LH ceiling” hypothesis explains the upper limit of responsiveness to LH for each follicle. Administration of LH beyond the upper limit results in follicle degeneration. Ceiling concentration for dominant follicle is higher than nondominant follicles.\textsuperscript{[33]} According to the concept of “therapeutic window for LH,” low-dose stimulation with LH improves steroidogenesis without inhibitory effect on cell proliferation; however, administration of high dose results in inhibition of granulosa proliferation, immature follicle atresia, and premature luteinization of preovulatory follicles.\textsuperscript{[33,34]}

### Consensus statement

Overall review of literature does not show a significant difference in terms of quality of oocytes retrieved and embryos transferred, with urinary versus recombinant gonadotropins.
Cost-effective analysis
A retrospective study in Chinese infertility patients (n = 1246) has shown that in IVF/ICSI treatment cycles, the use of HP-FSH results in lower financial burden compared to the use of rFSH.[32]

A randomized study evaluated the cost-effectiveness of uFSH versus rFSH. The investigators showed that both FSH have the same effectiveness in ovarian stimulation in intrauterine insemination (IUI) cycles in PCOS patients. However, the uFSH is more cost-effective because of the difference in their cost per IU. Similarly, the production of rFSH has higher medical costs.[35]

Another related study in 67 infertile patients showed similar results, i.e., more cost-effectiveness of urinary preparation (due to the difference of its cost per IU) with equal efficacy as compared to rFSH in ovarian stimulation in IUI cycles.[36]

Meta-analysis and Cochrane reviews have also concluded that the clinical choice of gonadotropin should depend on availability, convenience, and cost.[17‑19]

Consensus statement
Cost should be an important factor guiding choice of a particular gonadotropin. Urinary gonadotropins are more cost-effective than recombinant.

Route of administration
Although subcutaneous route of injection is convenient for self-administration, patients with infertility usually visit either the doctor or paramedical personnel for administration of injections. Considering the overall management scenario, route of administration does not play a significant role in choosing a particular gonadotropin.

Consensus statement
Route of administration for infertility management does not play a significant role as patients usually visit the doctor or paramedical personnel for injections.

Biosimilars
Biosimilars are the biopharmaceutical formulations manufactured by copying complex recombinant, high-molecular weight products.[37] They may differ from the original product in composition, strength, and purity.[38] The manufacturing process of biosimilars is complex, unlike that for pharmaceutical generics. Even a minor alteration in the process of manufacturing may have a potential impact on the efficacy and safety of the product. Although biosimilars are thoroughly compared with their reference product, available assays may not guarantee equivalent and consistent safety and efficacy of a biosimilar product.[37] Considering these complexities, biosimilars and innovator products should not be substituted for each other. The clinician should decide the right choice between two products for the patient.[38]

Consensus statement
Biosimilars and innovator products should not be substituted for each other. The decision whether to use an innovator or a biosimilar product should be reserved to the discretion of the treating physician.

Conclusion
To summarize, currently available evidences do not show any difference between urinary and recombinant gonadotropins with respect to rates of implantation, clinical pregnancies, live births, miscarriage, and multiple pregnancies. The development of rhFSH was thought to be a breakthrough that would revolutionize the management of infertility. Although theoretically, the rationale appears appealing, a comprehensive review of the literature suggests that HP uFSH has a similar safety-efficacy profile as compared to rFSH in controlled ovarian stimulation. Based on the evidences, we can also conclude that urinary gonadotropins might be superior to the recombinant variety in certain clinical scenarios such as advanced maternal age. There is also a need for gynecologists and infertility specialists to have a better understanding of biosimilars. In conclusion, we feel that choice of a gonadotropin should depend on overall cost of therapy, patient affordability, and availability.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References
1. Sharma R, Biedenharn KR, Fedor JM, Agarwal A. Lifestyle factors and reproductive health: Taking control of your fertility. Reprod Biol Endocrinol 2013;11:66.
2. Adamson PC, Krupp K, Freeman AH, Klausner JD, Reingold AL, Madhivanan P, et al. Prevalence and correlates of primary infertility among young women in Mysore, India. Indian J Med Res 2011;134:440-6.
3. Ganguly S, Unisa S. Trends of infertility and childlessness in India: Findings from NFHS data. Facts Views Vis Obgyn 2010;2:131-8.
4. Arora P, Polson DW. Diagnosis and management of premature ovarian failure. Obstet Gynecol 2011;13:67-72.
5. Leão Rde B, Esteves SC. Gonadotropin therapy in assisted reproduction: An evolutionary perspective from biologics to biotech. Clinics (Sao Paulo) 2014;69:279-93.
6. Crowe SJ, Cushing H, Homans J. Experimental hypophysectomy. Bull Johns Hopkins Hosp 1910;21:127-67.
7. Ascheim S, Zondek B. Hypophysenvorderlappenhormone und ovarialhormone im Harn von Schwangeren. Klin Wochenschr 1927;6:13-21.
8. Zondek B. Ueber die hormon des hypophysenvorderlappens. Klin Wochenschrift 1930;9:245-8.
9. Lunenfeld B. Historical perspectives in gonadotrophin therapy. Hum Reprod Update 2004;10:453-67.
10. Zwart-van Rijkom JE, Broekmans FJ, Leufkens HG. From HMG through purified urinary FSH preparations to recombinant FSH: A substitution study. Hum Reprod 2002;17:857-65.
11. Koulianos G. Gonadotropins in the treatment of infertility. US Obstet Gynecol 2009;4:29-36.
12. Foutouh IA, Khattab S, Mohsen IA, Moaz M, Al-Inany H. Clinical outcome following stimulation with HMG versus highly purified rFSH in patients undergoing ICSI. Reprod Biomed Online 2007;14:145-7.
13. Pacchiarotti A, Aragona C, Gaglirone R, Selman H. Efficacy of a combined protocol of urinary and recombinant follicle-stimulating hormone used for ovarian stimulation of patients undergoing ICSI cycle. J Assist Reprod Genet 2007;24:400-5.
14. Yarali H, Bukulmez O, Gurgan T. Urinary follicle-stimulating hormone (FSH) versus recombinant FSH in clomiphene citrate-resistant, normogonadotropic, chronic anovulation: A prospective randomized study. Fertil Steril 1999;72:276-81.
15. de Leeuw R, Mulders J, Voortman G, Romeut F, Damm J. Recombinant versus urinary‑derived FSH: An update. Mol Hum Reprod 1996;2:361-9.
16. Amer S. Gonadotropin induction of ovulation. Obstet Gynaecol Reprod Med 2007;17:205-10.
17. van Wely M, Kwan I, Burt AL, Thomas J, Vail A, Van der Veen F, et al. Recombinant versus urinary gonadotrophin for ovarian stimulation in assisted reproductive technology cycles. Cochrane Database Syst Rev 2011;9:CD005354.
18. Weiss NS, Nahuiss M, Bayram N, Mol BW, Van der Veen F, van Wely M, et al. Gonadotrophins for ovulation induction in women with polycystic ovarian syndrome. Cochrane Database Syst Rev 2015;9:CD010290.
19. Al-Inany H, Aboulghar M, Mansour R, Serour G. Meta-analysis of recombinant versus urinary-derived FSH: An update. Hum Reprod 2003;18:305-13.
20. Al-Inany HG, Abou-Setta AM, Aboulghar MA, Mansour RT, Serour GI. Efficacy and safety of human menopausal gonadotropins versus recombinant FSH: A meta-analysis. Reprod Biomed Online 2006;18:81-8.
21. Mohamed MA, Sbracia M, Pacchiarotti A, Micura G, Linari A, Tranquilli D, et al. Urinary follicle-stimulating hormone (FSH) is more effective than recombinant FSH in older women in a controlled randomized study. Fertil Steril 2006;85:1398-403.
22. Ye H, Huang GN, Cao YX, Zhong Y, Huang YH, Zhu GJ, et al. Effect of domestic highly purified urinary follicle stimulating hormone on outcomes of in vitro fertilization-embryo transfer in controlled ovarian stimulation. Zhonghua Fu Chan Ke Za Zhi 2013;48:838-42.
23. Liu X, Hao C, Wang J. Efficacy of highly purified urinary FSH versus recombinant FSH in Chinese women over 37 years undergoing assisted reproductive techniques. Int J Fertil Steril 2015;8:385-92.
24. Hedon B, Out HJ, Hugues JN, Camier B, Cohen J, Lopes P, et al. Efficacy and safety of recombinant follicle stimulating hormone (Puregon) in infertile women pituitary-suppressed with triptorelin undergoing in vitro fertilization: A prospective, randomized, assessor-blind, multicentre trial. Hum Reprod 1995;10:3102-6.
25. Ng EH, Lau EY, Yeung WS, Ho PC. HMG is as good as recombinant human FSH in terms of oocyte and embryo quality: A prospective randomized trial. Hum Reprod 2001;16:319-25.
26. Streher E, Abt M, El-Danasouri I, De Santo M, Sterzik K. Impact of recombinant follicle-stimulating hormone and human menopausal gonadotropins on in vitro fertilization outcome. Fertil Steril 2001;75:332-6.
27. Selman HA, De Santo M, Sterzik K, Cecchia E, El-Danasouri I. Effect of highly purified urinary follicle-stimulating hormone on oocyte and embryo quality. Fertil Steril 2002;78:1061-7.
28. Balasch J, Peñarrubia J, Fabregues F, Vidal E, Casamitjana R, Manau D, et al. Ovarian responses to recombinant FSH or HMG in normogonadotropic women following pituitary desensitization by a depot GnRH agonist for assisted reproduction. Reprod Biomed Online 2003;7:35-42.
29. Cheon KW, Byun HK, Yang KM, Song IO, Choi KH, Yoo KI, et al. Efficacy of recombinant human follicle-stimulating hormone in improving oocyte quality in assisted reproductive techniques. J Reprod Med 2004;49:733-8.
30. Kemeter P, Stroh-Weigert M, Feichtinger W. Ovarian stimulation with Urofollitropin (uFSH) results in a lower yield of oocytes compared to recombinant FSH (rFSH), nevertheless, uFSH is at least as effective as rFSH in younger patients: Preliminary results of a retrospective study with antagonist protocols in an IVF/ICSI Program. Open Reprod Sci J 2013;5:1-16.
31. Fovold HL. Synergism of follicle stimulating and lutetizing hormones in producing estrogen secretion. Endocrinology 1941;28:33-6.
32. Alivaggi C, Humaidan P, Howles CM, Tredway D, Hillier SG. Biological versus chronological ovarian age: Implications for assisted reproductive technology. Reprod Biol Endocrinol 2009;7:101.
33. Kumar P, Sait SF. Luteinizing hormone and its dilemma in ovulation induction. J Hum Reprod Sci 2011;4:2-7.
34. Fischer R. Understanding the role of LH: Myths and facts. Reprod Biomed Online 2007;15:468-77.
35. Gerli S, Casini ML, Unfer V, Costabile L, Mignosa M, Di Renzo GC, et al. Ovulation induction with urinary FSH or recombinant FSH in polycystic ovary syndrome patients: A prospective randomized analysis of cost-effectiveness. Reprod Biomed Online 2004;9:494-9.
36. Gerli S, Casini ML, Unfer V, Costabile L, Bini V, Di Renzo GC, et al. Recombinant versus urinary follicle-stimulating hormone in intrauterine insemination cycles: A prospective, randomized analysis of cost-effectiveness. Fertil Steril 2004;82:573-8.
37. Locatelli F, Roger S. Comparative testing and pharmacovigilance of biosimilars. Nephrol Dial Transplant 2006;21 Suppl 5:v13-6.
38. Orvieto R, Seifer DB. Biosimilar FSH preparations- are they identical twins or just siblings? Reprod Biol Endocrinol 2016;14:32.