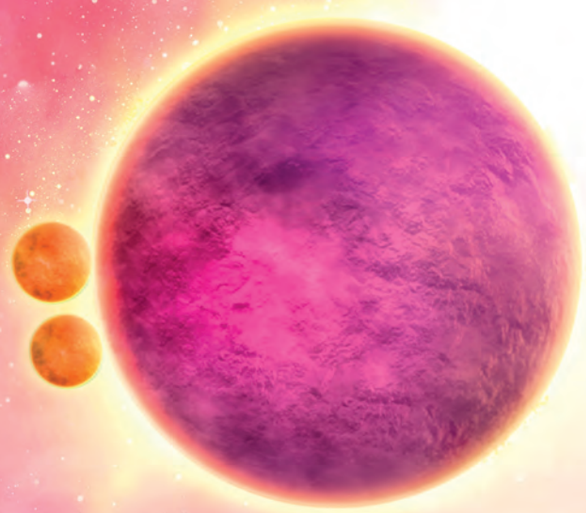
Fostimon®

Highly Purified hFSH

Origins of life

Following nature's model.



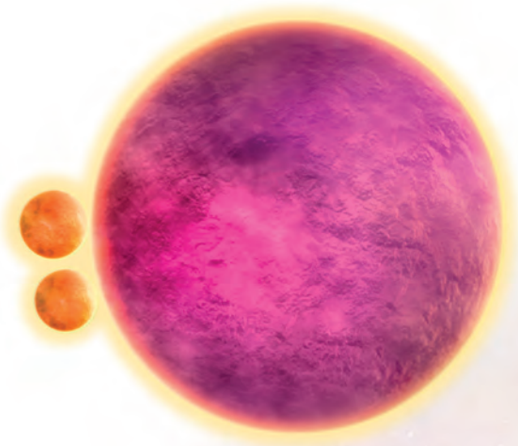
Prescribing information on page 19.

IBSA

Caring Innovation

* See table of Fostimon® Clinical Studies on pages 16, 17

Fostimon® | Highly Purified hFSH



Introducing an innately human essence of the highest quality in ART programs.

EXCLUSIVE

Recognising the crucial importance of glycosylation in FSH, IBSA developed and patented a non-aggressive purification system to obtain a full range of FSH isoforms at the highest purity[1,2].

NATURE-INSPIRED

IBSA's highly purified FSH is rich in highly glycosylated (acidic) isoforms[2]. In a natural cycle, these isoforms predominate in the early follicular phase and are essential for effective recruitment and optimal maturation of oocytes[3-5].

RELIABLE

Over fifteen years of clinical experience and randomised, controlled clinical studies confirm that **Fostimon®** is an effective and reliable alternative to existing FSH preparations.*

IBSA

Follicle-stimulating hormone (FSH)

Follicle-stimulating hormone (FSH) is a major player in folliculogenesis and oocyte maturation. FSH binds to its ovarian receptor to sustain oocyte maturation up to the release of a single mature oocyte.
Other FSH actions include stimulation of steroidogenesis resulting in estrogen production, granulosa cell proliferation, induction of luteinising hormone receptors (LH-R) and its own receptors (FSH-R)[6].

FSH can be used as therapeutic support to induce the maturation of single or multiple follicles as part of assisted reproduction programs.
(Fostimon® Smpc)

FSH structure

FSH is a complex glycoprotein made of a proteic part and a glycidic part (carbohydrate), which is about 30% of its molecular mass. The proteic part is composed by two non-identical α and β subunits: β accounts for the specific biological properties of FSH. Each proteic subunit has two possible N-linked glycosylation sites (Figure 1) for the carbohydrate. Consequently, FSH exists as a family of **isohormones or isoforms**, which differ in their ionic charge due to variance in their carbohydrate structure, including variations in the total number of charged terminal sialic acid and, to a lesser extent, the sulphate residues[7].

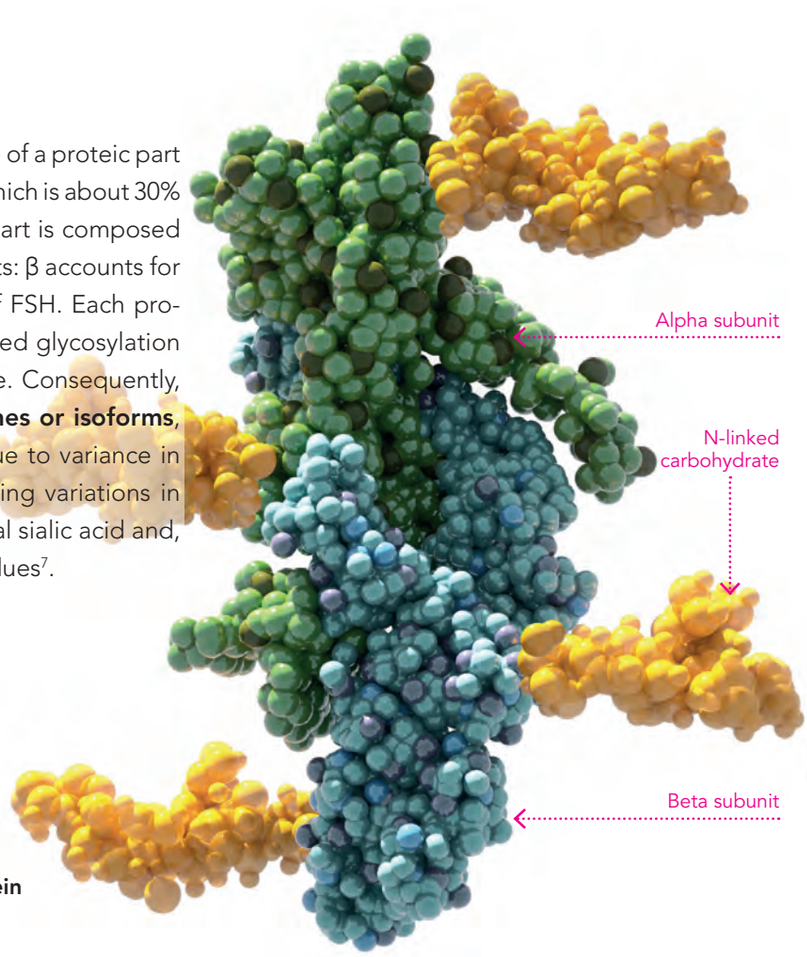


Figure 1. FSH is a complex glycoprotein
(Adapted from textual data)[7]

HIGHLIGHT

FSH is a complex glycoprotein, existing as a family of isoforms, which differ in their ionic charge due to great variance in their carbohydrate structure[7].

FSH isoform (FSH)

The carbohydrates characterise the different isoforms (Figure 2): they are actually made of a sequence of sugars; in particular, there is a 'core' of mannose with 1 to 4 branches or antennae made of N-acetyl glucosamine, galactose and sialic acid.

The pituitary gland releases **highly glycosylated and low glycosylated (acidic or less acidic) isoforms depending on the sialic content**, with different degrees of complexity of the carbohydrate branching pattern. Nature's several combinations of carbohydrate structures thus occur, playing a key role in determining the different functional properties of FSH. The carbohydrate structure characterises these different FSH **isoforms** and affects and modulates the affinity of FSH for its receptor[8].

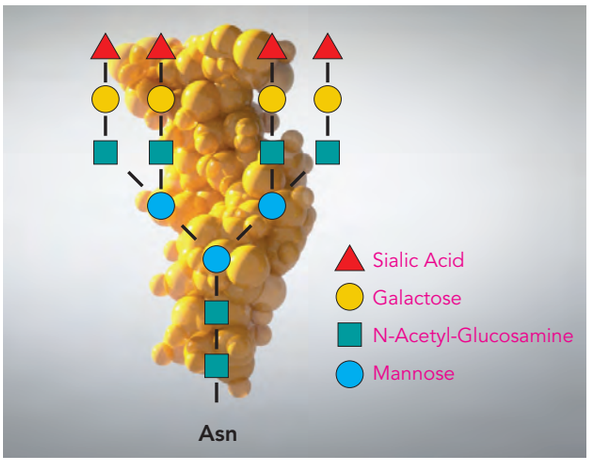


Figure 2. Schematic representation of the carbohydrate chains of the FSH molecule (Adapted from textual data)[8]

The higher the number of branches and of sialic acid molecules, the higher the acidity of the molecule (Figure 3). Actually, the anterior pituitary gland produces a mix of differently glycosylated/sialylated isoforms, covering a wide range of acidity.

Depending on their sialic content, the potential of these naturally occurring isoforms to evoke a specific effect at the target cell level may differ. Studies in a variety of species and in humans have clearly demonstrated this heterogeneity of FSH[3].

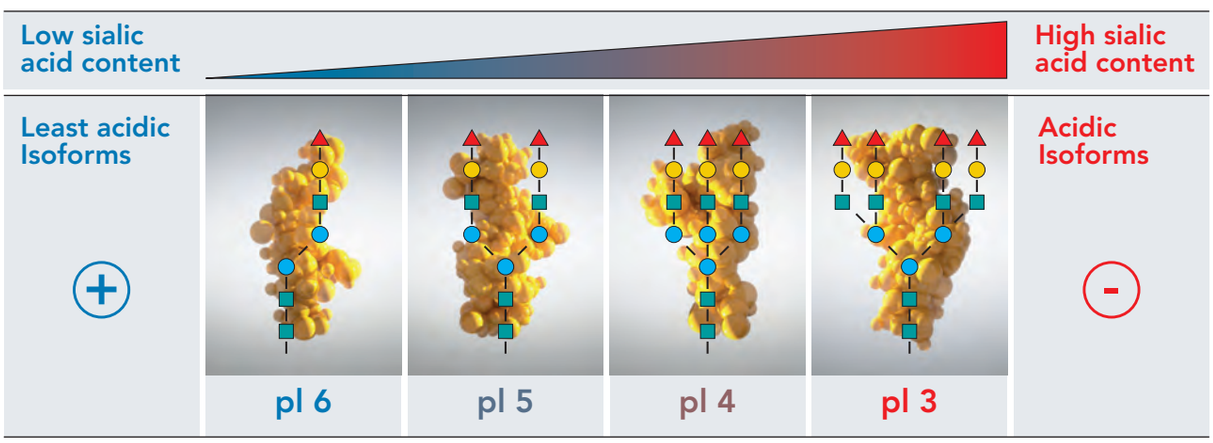


Figure 3. Schematic representation of human pituitary range of FSH isoforms according to the isoelectric point (pI) (Adapted from textual data)[3]

In IBSA's human Highly Purified FSH (hFSH), specific analyses have shown a predominance of highly sialylated, highly branched carbohydrates as compared to recombinant FSH (rFSH) expressed in rodent cell lines.

The antennary structure is crucial for many *in vivo* biological activities of hFSH, regulating folding, secretion, immunogenicity, and plasma half-life, as well as modulating some biological behaviors[2].

Half-life of FSH isoforms

The glycosylation and specifically the content at sialic acid of FSH isoforms directly correlate with their half-life. The more glycosylated and sialylated isoforms have shown a significantly longer half-life *in vivo*[9,10], due to a reduced first pass hepatic catabolism: the sialic acid 'cap' prevents hepatic degradation of the carbohydrate moiety, thus conferring higher bio-availability to the FSH molecule and allowing higher circulating levels (Figure 4).

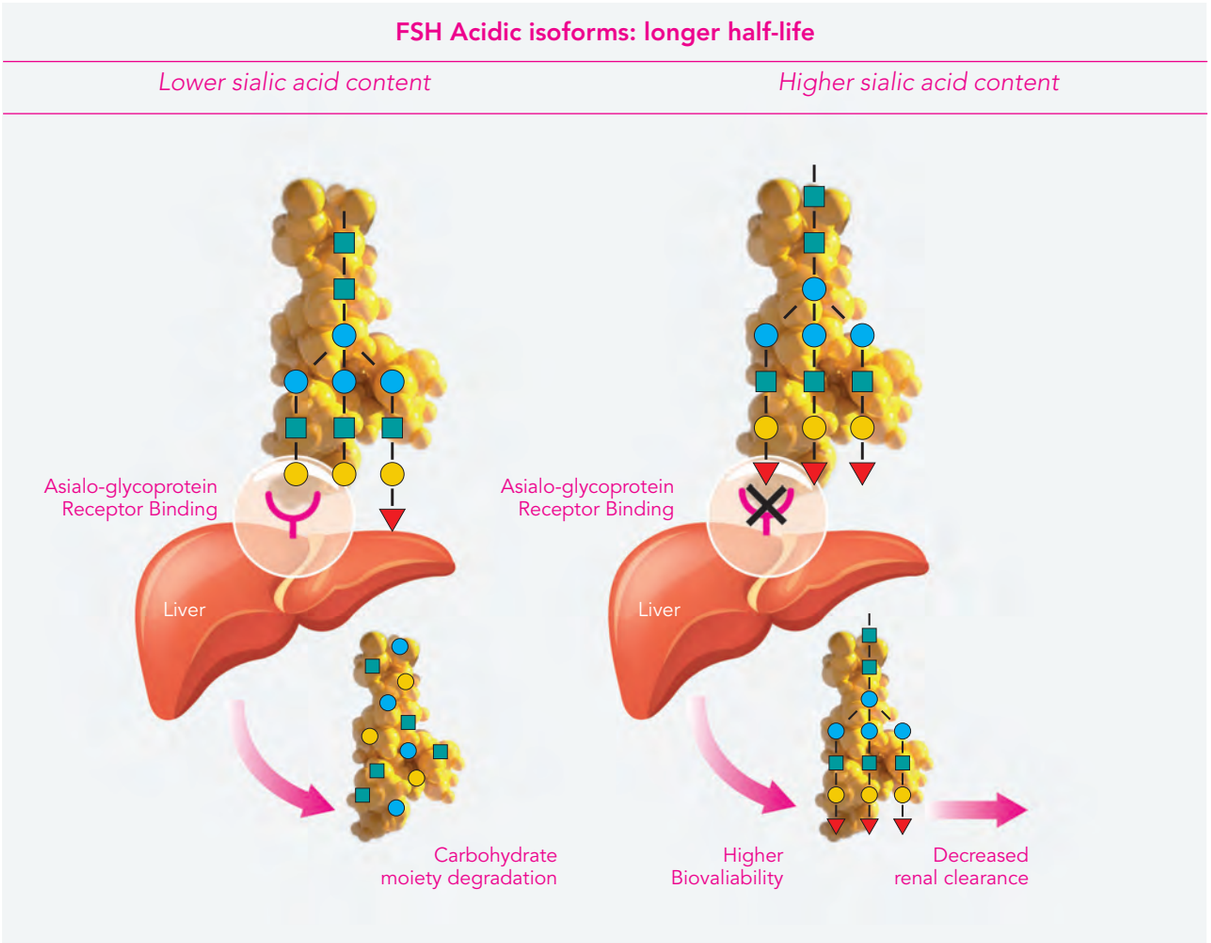


Figure 1. Schematisation of the metabolic pathway of non-acidic and acidic FSH molecules
(Adapted from textual data)[9,10]

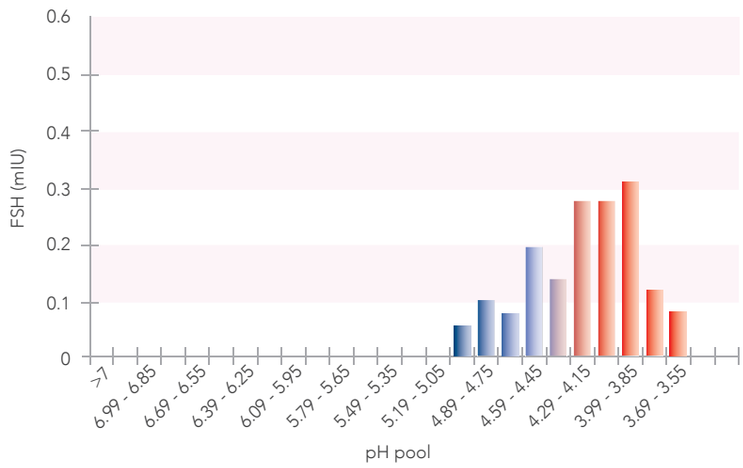
HIGHLIGHT

The carbohydrate chains play a key role in determining the different functional properties of the FSH molecule, including metabolic clearance (half-life) and are important for determining receptor-binding affinity and receptor activation[9,10].

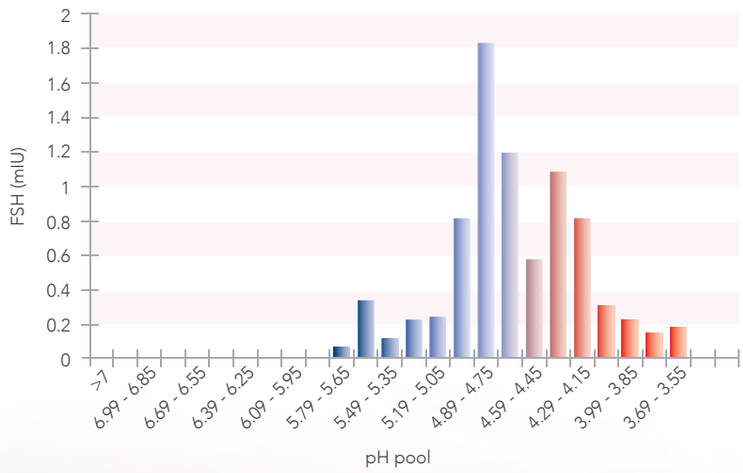
The changing FSH isoform profile during the menstrual cycle

Highly glycosylated, acidic isoforms are predominantly released in the early follicular phase and drop approaching ovulation to progressively rise back during the luteal-follicular transition. On the other hand, **less acidic isoforms are more common as ovulation approaches**[4] (Figure 5).

Early-mid follicular phase



Midcycle



Charged distribution of FSH by chromato-focusing of serum samples taken from one woman at different stages of her menstrual cycle[8].

Figure 5. Isoform distribution of FSH at different stages of the menstrual cycle (Adapted from Anobile 1998)[4]

More acidic isoforms are required for effective recruitment and optimal maturation of oocytes, while the less acidic isoforms are physiologically relevant in the periovulatory period and are significantly more effective in stimulating the synthesis and secretion of estrogens[4,5].

It is the increase in estrogen levels in the preovulatory phase of the menstrual cycle that drives the shift from the secretion of acidic FSH isoforms to isoforms with relatively low sialic acid content (Figure 6). It has been shown that during the mid-cycle phase of the normal cycles there was a shift of FSH isoforms (as measured by immunoassay) to the basic pH range. In contrast, in the mid- to late luteal phase there was an increase in FSH isoforms in the acidic pH range. Therefore, it appears that estrogenic stimulation causes preferential secretion of less acidic isoforms with increased biological activity[11,12].

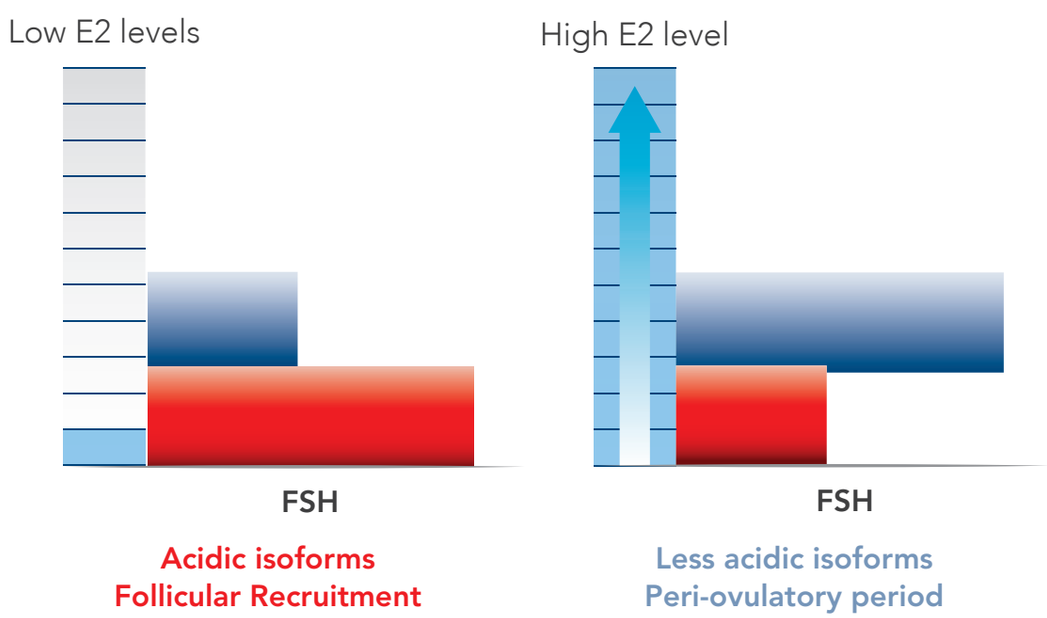


Figure 6. Schematic representation of estrogen levels during the menstrual cycle and natural pattern of release of FSH isoforms (Adapted from textual data)[11]

The increase in estrogen levels drives the shift from the more acidic isoforms to the less acidic isoforms as ovulation approaches[11].

Role of different FSH isoforms

Proper follicular development probably depends on specific and timely exposure to particular FSH isoform mixtures[5].

Acidic isoforms

When sustained gonadal stimulation is essential, such as during the early follicular phases of menstrual cycles - when follicular recruitment and growth of the follicle are occurring - a more acidic mix of FSH isoforms prevails in the circulation. It has been shown that acidic isoform mixtures actually **facilitate ovarian follicular maturation**[11,13]. Acidic isoforms of FSH, compared to less acidic ones, induce **greater production of inhibin,** which exerts a negative feedback on the pituitary, thereby producing less FSH and and allowing for a fine-tuning of the follicular maturation and the recruitment of fewer but better selected follicles[3].

Less acidic isoforms

During the periovulatory period, a significant increase in secretion of less acidic isoforms has consistently been observed. This means that, at times **when an acute and potent signal is essential to accelerate the growth of the pre-ovulatory follicle, increased proportions of less acidic FSH isoforms are present** in the circulation[11,13].

It has been demonstrated that FSH isoforms with pI >5.0 induced resumption of meiosis more efficiently than acidic isoforms. Studies in animal models have shown that the low concentrations of less acidic isoforms produce the most rapid growth of follicles[7], and that follicles exposed to the low levels of less-acidic isoforms result in rapid development of two-cell embryos in 80% of the oocytes, after subsequent *in vitro* maturation[5].

Thus, resumption of meiosis seems to be synergistic with final pre-ovulatory follicle maturation.

SUMMARY[3,5,7,11-13]

Natural pattern of release of FSH isoforms during the menstrual cycle

FSH isoforms	Acidic isoforms	Less acidic isoforms
Acidic isoforms during follicular recruitment	Sustained stimulation of follicles	Acute & potent stimulation
Less acidic isoforms before ovulation	Longer half-life	Massive estrogen production
Estrogen level-driven shift	Growth and maturation	Resumption of meiosis

A nature-inspired model

The divergent effects of acidic and less acidic isoforms may be **critical for a more precise regulation of the ovarian response to the gonadotropic stimulus *in vivo*,** allowing for an optimal follicular development[3,5].

Consequently a Nature-inspired model of COH, foreseeing the use of a wide range of FSH isoforms, may also be beneficial for:

- Oocyte quality
- Endometrial coordination

Oocyte quality

There is a strong link between follicular growth and oocyte development: in the animal model, it was shown that the role of FSH in the acquisition of the oocyte developmental competence is primarily associated with its effects on follicular growth.

Indeed, the oocyte quality depends on which and how much genetic information the oocyte may accumulate before germinal vesicles breakdown (Figure 7). **The optimal oocyte quality requires perfect follicular timing and differentiation[14,15].**

Oocyte's transcription silencing
Schematic representation of genetic activities (transcription in blue dotted line) in the oocyte during follicular differentiation.

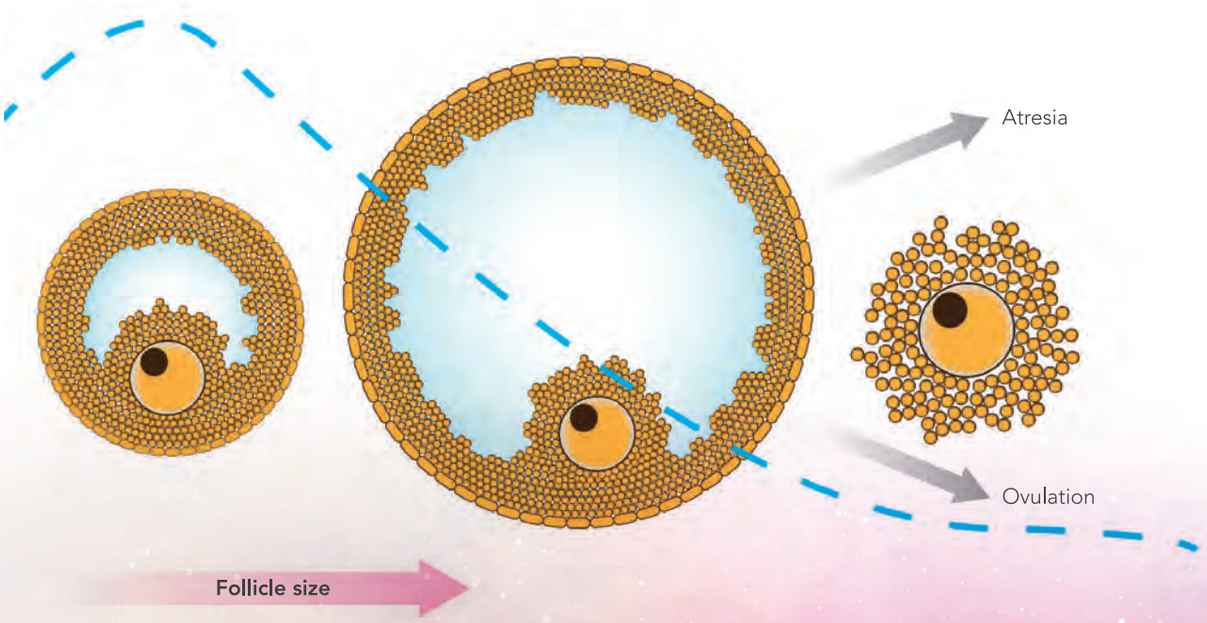


Figure 7. (Adapted from Sirard 2012)[14]

The timely exposure to mixtures of different FSH isoforms mixtures has an impact on follicular development:

• It has been shown that follicular development results in **oocytes with a superior developmental competence when the action of less acidic isoforms is accompanied by the presence of more acidic isoforms**[5]**.**

• On the other hand, findings have shown that continuing exposure to less acidic isoforms only, without the buffering effect of other isoforms, may be detrimental for embryo development[5,16,17].

• Exposure to relative high concentrations of less acidic isoforms *in vitro* may result in disorganized follicular development that causes inability to sustain proper oocyte maturation, with a detrimental effect on embryo development[5,16].

Endometrial coordination

Less acidic isoforms exhibit a lower dissociation constant to their cognate receptor, which may explain the greater capacity to stimulate estrogen production by granulosa cells[3].

The majority of implantation failures after conventional controlled ovarian stimulation (COS) are due to endometrial impairment from COS itself. One possible mechanism of impairment is the advancement of the receptive phase, which results in embryo–endometrium asynchrony[18,19]**.**

The impact of ovarian stimulation on endometrial receptivity is critical. Abnormal concentrations of estrogens and progesterone secondary to ovarian stimulation might affect the endometrial morphology and thereby the endometrial receptivity[19].

An early and massive production of estrogens (E) during the early follicular phase may contribute to changes in the endometrium leading to this embryo-endometrial asynchrony[18,19].
In the natural model, the gradual E increase ensured by acidic FSH isoforms might allow for adeguate coordination of the endometrial preparation, thus possibly favouring implantation.

SUMMARY[3,5,14-19]

Oocyte/ embryo quality	E elevation in follicular phase	Endometrial coordination
Mix of isoforms are needed for good developmental competence	Early E elevation due to eccessive FSH	Early rise of E determines asynchrony of embryo-endometrium development

Less acidic FSH isoforms induce even more E.

Acidic FSH isoforms in the follicular phase allow for more gradual E increase

Fostimon® purification process: the IBSA innovation

There are two main variables that influence the glycosylation content in the final FSH products[20]:

- the type of raw material to be purified
- the purification process

Recombinant FSH

In recombinant FSH (recFSH), the level of glycosylation of the final product is influenced by the nature of the starting material to purify.

The FSH proteic α and β subunits are produced within the cell ribosomes and their aminoacidic sequence is genetically encoded; this means that inserting the gene of the human FSH in laboratory cell lines, such as the Chinese hamster ovary (CHO) cells, the α and β subunits can be entirely replicated[20].

On the other hand, **the glycidic part of the glycoprotein, the carbohydrate chains, are produced and attached to the proteins in the Golgi apparatus and this step totally depends on the cell enzymatic pool[21].** (Figure 8)

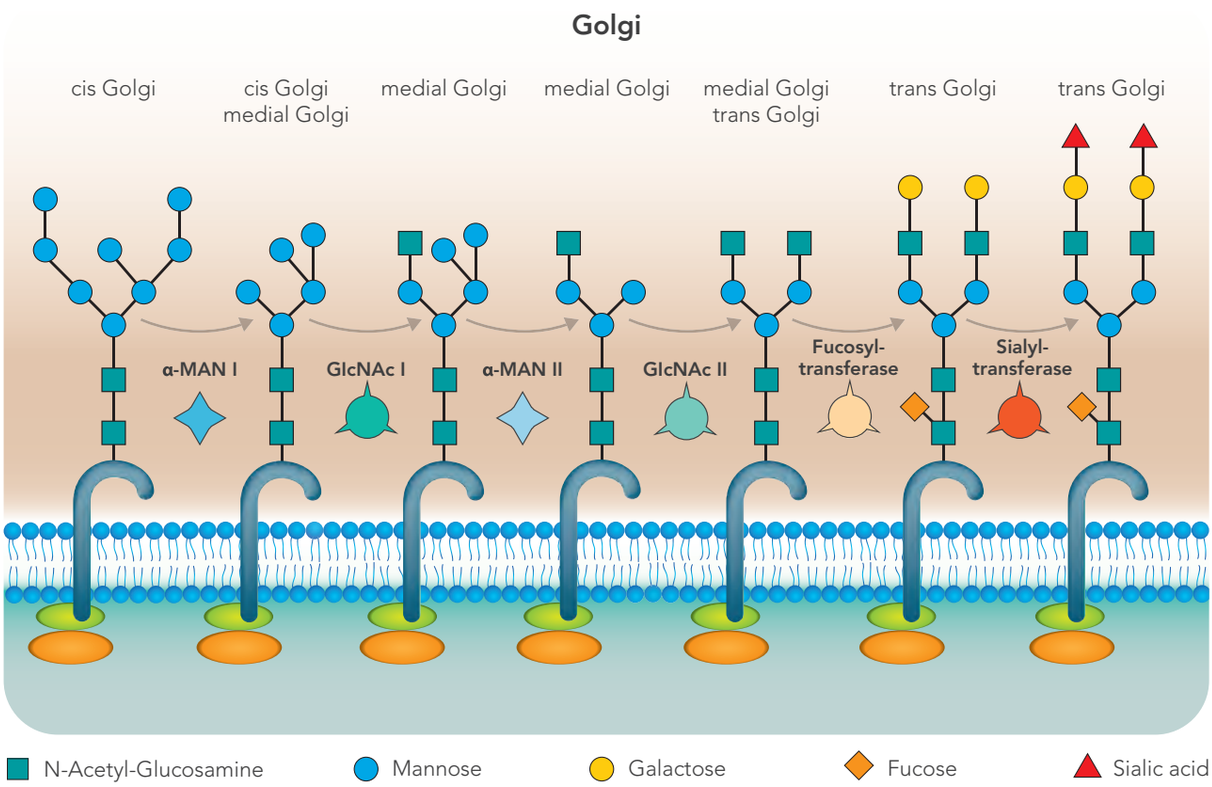
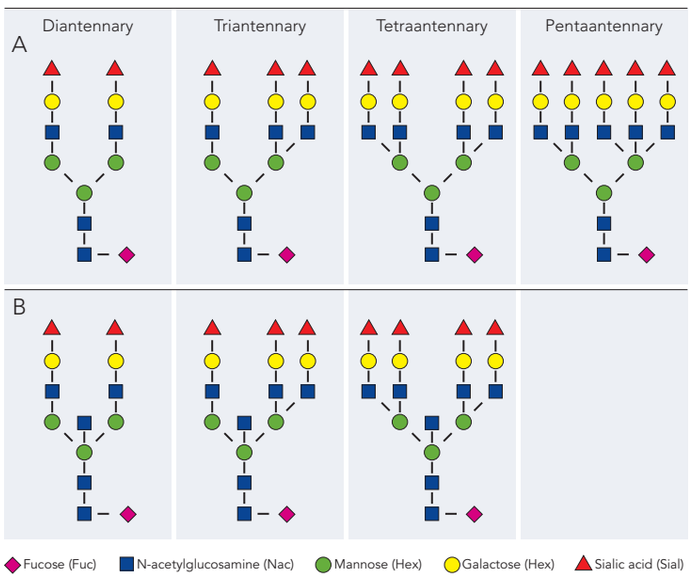


Figure 8. The proteic subunits α and β are glycosylated by the cellular enzymes
(Adapted from textual data)[21]

The resulting glycosylation process is species-specific, entirely depending on the type of enzymatic pool of the producing cells. Rodent cells, which are typically used to produce recombinant FSH, have a different enzymatic machinery compared to human cells.

The rec-FSH produced by CHO cells therefore exhibits less branched carbohydrate structures than pituitary and extracted FSH[2].
In other words, rec-FSH has the same proteic backbone of the human-derived FSH, but is poorer in carbohydrate chains antennarity. (Figure 9).



A) Complete antennary structures of N-glycans in hFSH α- and β-subunits.

B) Bisecting antennary structures, which may derive from the lack of one Hex in the complete structures.

Figure 9. (Adapted from Lombardi 2013)[2]

Due to its content in low-glycosylated forms, rec-FSH isoform distribution is in the range of the less acidic isoforms[2].

Extractive FSH

In the case of extractive FSH, the final glycosylation range is mainly affected by the purification process.

There is a specific pattern of release of different FSH isoforms during a woman's reproductive life. It is well known that with aging the ovary produces increasing amounts of FSH, with increasing mean levels of glycosylation. At the time of menopause, almost all circulating FSH is highly glycosylated and more acidic[2,12].

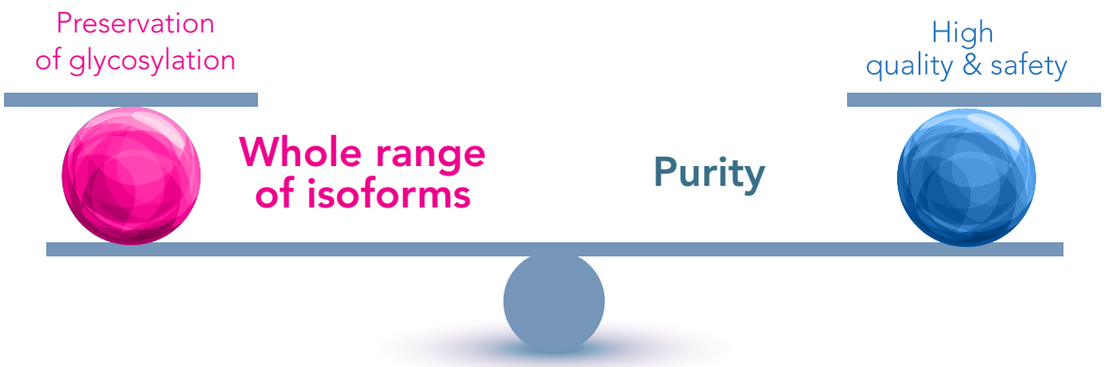
IBSA's extractive FSH is produced exclusively by human cells and extracted from menopausal women's urines, and is therefore rich in glycosylated acidic FSH isoforms[2,34].

For many years, the development of gonadotropin drug products was driven by the need of increasing purity, whereas little attention was paid to the level of glycosylation of the molecules. While purity is not an issue anymore, the ordinary urine purification process to obtain extractive FSH is complex and may cause the detachment of the sugars.

IBSA's purification process

Recognising the critical importance of sugars in the FSH molecules, IBSA developed and patented a new purification process that preserves glycosylation[1].

The challenge is to maintain high purity and quality, while preserving glycosylation in adequate balance.



IBSA's approach has been to develop a new, patented purification process using state-of-the-art technology and know-how.

Under the same global quality assurance system, the all-in-house workflow includes:

Urine collection

Early purification

Final purification

HIGHLIGHT

IBSA's approach is a new, patented purification process that leverages on the best-advanced technologies and know-how. IBSA's innovative purification process preserves the whole range of natural FSH isoforms, while guaranteeing the maximal level of purity[2].

Ibsa's purification protocol is a non-aggressive two-step process, based on selective precipitation and solubilisation steps to eliminate contaminants, while preserving the structure of gonadotropins.

Step 1: Early purification

The initial purification is aimed at reducing the load of proteins, by exploiting the chemical properties of the molecules. It consists of a non-aggressive process, based on selective precipitation and solubilisation steps to eliminate other components of the solution, preserving the inner structure of FSH and its isoforms (figure 10). This avoids the use of further aggressive chemicals to reach the targeted purity, preventing the loss of sugars, which are critical to final product quality.

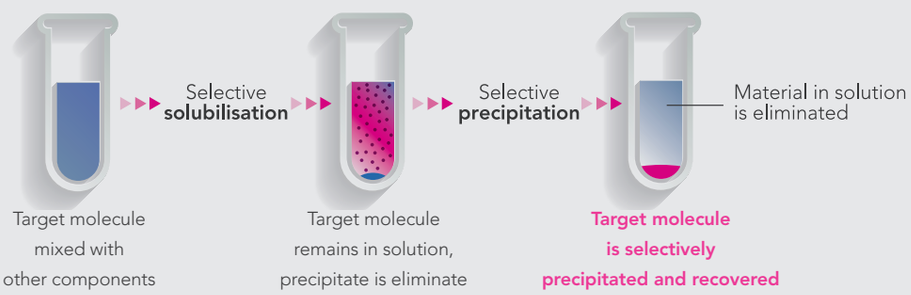


Figure 10.

Step 2: Final purification

The final purification steps include a series of cromatographies that allow for recovery of the whole range of FSH isoforms, excluding impurities.

The most important **high affinity chromatography** is based on a **blue sepharose resin, an innovation in the approved patent** that enables high selectivity in fractionating the different protein species and **extended recovery of all FSH species (including very acidic isoforms), thereby ensuring a high purification yield.**

FSH isoform range

By implementing its patented purification process that preserves the sugar moieties, Fostimon® appears to contain more highly glycosylated FSH molecules (more acidic isoforms) than recombinant FSH products[2].

The oligosaccharide composition of commercial follicle stimulating hormone preparations has been evaluated[2]. Technological improvements in analytical techniques and bioinformatics enabled characterising both both the α- and β-subunits of urinary human FSH (Fostimon®) in comparison with recombinant hFSH (recFSH)[2].

Isoelectrofocusing (IEF) analysis was performed, in order to compare hFSH of different origin. Differences in the net charge distribution were observed, as illustrated in Figure 11. Differences in the band distribution can be seen. Fostimon® showed bands in the more acidic region, whereas for the recFSH forms the bands were shifted toward the more basic region. These results demonstrate the prevalence in Fostimon® of more acidic isoforms, which correspond to species containing more sialylated and branched carbohydrate moieties. In contrast, the less acidic isoforms observed for recombinant FSH correspond to a lower content of sialic acid and a prevalence of diantennary species[2].

Lanes 1, 3, 5, 7:
pI marker (Serva).

Lane 2:
hFSH (Fostimon®, IBSA, Switzerland).

Lane 4:
recFSH (Gonal-f, Merck Serono, Switzerland).

Lane 6:
recFSH (Puregon, Organon, the Netherlands).

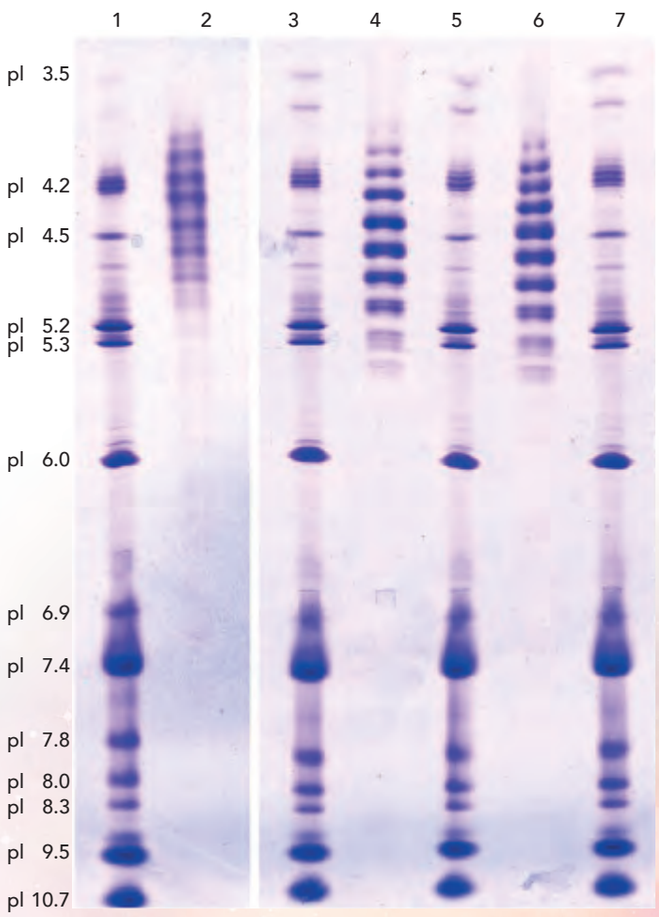


Figure 11. IEF separation of recombinant hFSH and urinary hFSH (Fostimon®) (Adapted from Lombardi 2013)[2]

The molecular species contained in Fostimon® were fully characterised, accurately recording the number of antennae, the composition and completeness of the carbohydrate moieties present in the FSH active compound. **All the results showed that Fostimon® contains a more sialylated, more branched distribution, compared to the commercially available hFSH from recombinant origin.**

These analyses prove that the protocol specifically designed to extract Fostimon® from human urine as a highly purified, pharmaceutical grade product preserves the glycosylation status of the molecule at every step and minimises the possible degradation of the oligosaccharide moieties[2].

The status of carbohydrate residues is essential for the *in vivo* biological activity of the gonadotrophins, because they regulate folding, secretion, and immunogenicity. Furthermore, they are essential for the plasma half-life of the glycoprotein hormones and for modulating some of the other biological behaviours of the hormone[2].

HIGHLIGHT

The differences in the glycosylation pattern of Fostimon® compared to other marketed products whose FSH is obtained from recombinant technologies are also likely to be reflected in different biological properties[2].

The quality of the final product

First author and year of publication	Patients number	Objectives	Conclusions
Selman, 2002[22]	267	To determine the **effects of ovarian stimulation with highly purified urofollitropin on oocyte and embryo quality**, in comparison with recombinant FSH.	Highly purified urinary FSH is as effective, efficient, and safe for clinical use as recombinant FSH.
Mohamed, 2006[23]	257	To determine which FSH, recombinant or urinary, works better in older women (>39 y).	Urinary **FSH performed better in older women than recombinant FSH** when associated with the long protocol.
Pacchiarotti, 2007[24]	119	To evaluate the efficacy of using both urinary and recombinant FSH in a combined protocol for ovarian stimulation in an IVF treatment program.	This study shows that **using a combination of both urinary and recombinant FSH** for ovarian stimulation improves oocyte maturity and embryo cleavage, and increases pregnancy and implantation rates compared to rec FSH alone.
Baker, 2009[25]	152	To compare the efficacy of highly purified human urinary follicle stimulating hormone (HP-hFSH) versus human recombinant follitropin-alpha (rFSH) in volunteers undergoing controlled ovarian stimulation for IVF.	There were **no statistically significant differences in mean oocyte number, clinical pregnancy rate, or live birth rate between HP-hFSH versus rFSH**.
Abate, 2009[26]	401	To evaluate the efficacy on oocyte and embryo quality in *in vitro* fertilisation/ intracytoplasmic sperm injection cycles, comparing human follicle stimulating hormone (hFSH) and recombinant FSH (rFSH).	Fertilisation, cleavage and implantation rates, pregnancy and abortion rates were similar in both groups. In our study, we demonstrated that **hFSH and rFSH products are equivalent in terms of clinical efficacy**. However a significantly higher nr of oocytes was retrieved and the total duration of stimulation and total IU used were significantly lower in Fostimon® group.
Selman, 2010[27]	188	To evaluate the impact of follicle-stimulating hormone (FSH) with different glycosylation patterns on oocyte quality and clinical outcomes in an *in vitro* fertilization (IVF) treatment program.	**The glycosylation patterns of the two types of FSH implemented for ovarian stimulation have different impacts on oocyte quality and clinical outcome. A sequential combined protocol using both acidic and less acidic FSH for ovarian stimulation improves oocyte maturity and embryo cleavage, and increases pregnancy and implantation rates.**
Aboulghar, 2010[28]	84	To compare highly purified urinary FSH with recombinant FSH in IVF/ ICSI cycles for patients with PCOS.	There was no significant difference between the mean total dose of FSH used, duration of stimulation, number of retrieved oocytes, number of mature oocytes, number of embryos transferred, or the ongoing pregnancy rate between the two groups. However, **there were significantly more fertilized oocytes, a higher fertilization rate, more top-quality embryos, and more cryopreserved embryos in the urinary FSH group**.

First author and year of publication	Patients number	Objectives	Conclusions
Murber, 2011[29]	70 cycles	To verify the impact of HP-FSH in comparison with rFSH on oocyte-, embryo quality and embryo development in IVF-ET+ICSI cycles.	There were no significant differences in clinical pregnancy and in live birth rates. Oocytes obtained with HP-FSH stimulation showed higher fertilisability, whereas pregnancy and live birth rates did not differ between the groups. However, **patients treated with HP-FSH may benefit from the higher rate of embryos capable for cryopreservation, suggesting that cumulative pregnancy rates might be higher in this group.**
Kemeter, 2013[30]	1051 cycles	**Differences in the mode of action between recombinant FSH (rFSH) and urinary derived FSH (uFSH) have been reported in cycles down-regulated by agonists. The aim of this study was to determine if these differences also exist in cycles down-regulated by antagonists.**	The results of this study seem to support the concept that uFSH produces fewer oocytes than rec-FSH, but of better quality. Preclinical studies have shown that different FSH isoforms with different elimination kinetics in the two gonadotropin preparations could be responsible for the different effects.
Selman, 2013[31]	197	To evaluate the effect of a combined stimulation protocol of human FSH and recombinant FSH, simultaneously administered, on oocyte and embryo quality and clinical outcome.	**The results show that the combination of human and recombinant FSH for ovarian stimulation may produce a positive effect on follicular development as it improve oocyte quality, embryo development, and ultimately clinical outcome.**
Gurgan, 2014[32]	90	To find proposed biomarkers that might be used to predict and screen for oocyte quality, with the implication that this could also predict embryo quality.	Although there was a positive tendency in favor of the sequential treatment, there was no significant difference in pregnancy rates, even taking frozen embryos into consideration. **The cumulus cell transcriptome varied considerably between the treatments, although with no clear significance**.
Colacurci, 2014[33]	230	To investigate if a stimulation protocol using urinary-FSH during the early follicular phase and then shifting toward recombinant-FSH may improve oocyte quality and pregnancy rate in 35–40 years old patients in IVF program.	A sequential protocol using urinary- FSH in the early days of stimulation and subsequently recombinant-FSH may improve the IVF outcome in patients of advanced reproductive age. **The sequential protocol can be used as a specific procedure in those women undergoing IVF that need an improved oocytes quality**.

References

1. Italian patent no. 1287138 of 4.8.1998; European patent no. 0882064 of 9.4.2003.
2. Lombardi A *et al.*, Evaluation of the oligosaccharide composition of commercial follicle stimulating hormone preparations. Electrophoresis 2013;34(16): 2394-406.
3. Timossi CM *et al.*, Differential effects of the charge variants of human follicle stimulating hormone. J Endocrinol. 2000;165:193–205.
4. Anobile CJ *et al.*, Glycoform composition of serum gonadotrophins through the normal menstrual cycle and in the post-menopausal state. Mol Hum Reprod. 1998;4(7):631–9.
5. Andersen CY. Effect of FSH and its different isoforms on maturation of oocytes from pre-ovulatory follicles. Reprod Biomed Online. 2002;5(3):232-9.
6. Andersen CY *et al.*, Human steroidogenesis: implications for controlled ovarian stimulation with exogenous gonadotropins. Reprod Biol Endocrinol. 2014 28;12(1):128.
7. Andersen CY *et al.*, FSH-induced resumption of meiosis in mouse oocytes: effect of different isoforms. Mol Hum Reprod. 1999;5(8):726-31.
8. Ulloa-Aguirre A *et al.*, Impact of carbohydrate heterogeneity in function of follicle-stimulating hormone: studies derived from *in vitro* and *in vivo* models. Biol Reprod 2003;69:379–89.
9. Wide L. The regulation of metabolic clearance rate of human FSH in mice by variation of the molecular structure of the hormone. Acta Endocrinol. (Copenh) 1986;112(3):336-44.
10. Wide L *et al.*, Serum half-life of pituitary gonadotropins is decreased by sulfonation and increased by sialylation in women. J Clin Endocrin Metab. 2009;94(3):958-64.
11. Padmanabhan V *et al.*, Modulation of serum follicle-stimulating hormone bioactivity and isoform distribution by estrogenic steroids in normal women and in gonadal dysgenesis. J Clin Endocrinol Metab. 1988;67(3):465-73.
12. Wide L *et al.*, Effects of 17ß-oestradiol and norethisterone acetate on sulfonation and sialylation of gonadotrophins in post-menopausal women. Ups J Med Sci. 2010;115:97–106.
13. West CR *et al.*, Acidic mix of FSH isoforms are better facilitators of ovarian follicular maturation and E2 production than the less acidic. J Clin Endocrinol Metab. 2009;94(3):958-64.
14. Sirard MA *et al.*, *In vivo* and *in vitro* effects of FSH on oocyte maturation and developmental competence. Theriogenology. 2007;68 Suppl 1:S71-6.
15. Sirard MA. Factors affecting oocyte and embryo transcriptomes. Reprod Dom Anim 2012;47 (Suppl. 4): 148–55.
16. Vitt UA *et al.*, Isoforms of human recombinant follicle-stimulating hormone: comparison of effects on murine follicle development *in vitro*. Biol Reprod. 1998;59:854–61.
17. Nayudu PL Intact follicle culture: what it can tell us about the roles of FSH glycoforms during follicle development. Reprod Biomed Online. 2002;5(3):240-53.
18. Shapiro BS *et al.*, Evidence of impaired endometrial receptivity after ovarian stimulation for *in vitro* fertilization: a prospective randomized trial comparing fresh and frozen–thawed embryo transfer in normal responders. Fertil Steril 2011;96(2):344-8.
19. Fatemi HM and Popovic-Todorovic B. Implantation in assisted reproduction: a look at endometrial receptivity. 2013; Reprod BioMed Online 2013;27:530–8.
20. Andersen CY *et al.*, FSH isoform composition of commercial gonadotrophin preparations: a neglected aspect? Reprod Biomed Online. 2004;9(2):231-6.
21. Spiro RG. Protein glycosylation: nature, distribution, enzymatic formation, and disease implications of glycopeptide bonds. Glycobiol. 2002;12(4):42R-56R.
22. Selman HA *et al.*, Effect of highly purified urinary follicle stimulating hormone on oocyte and embryo quality. Fertil Steril. 2002;78(5):1061-7.
23. Mohamed MA *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(5):1398-403.
24. Pacchiarotti J *et al.*, Efficacy of a combined protocol of urinary and recombinant follicle-stimulating hormone used for ovarian stimulation of patients undergoing ICSI cycle. Assist Reprod Genet. 2007;24(9):400-5.
25. Baker VL *et al.*, Clinical efficacy of highly purified urinary FSH versus recombinant FSH in volunteers undergoing controlled ovarian stimulation for *in vitro* fertilization: a randomized, multicenter, investigator-blind trial. Fertil Steril. 2009;91(4):1005-11.
26. Abate A *et al.*, Efficacy of recombinant versus human derived follicle stimulating hormone on the oocyte and embryo quality in IVF-ICSI cycles: Randomised controlled, multi-centre trial. Gynecol Endocrinol. 2009;25(8):479-84.
27. Selman HA *et al.*, Ovarian stimulation protocols based on follicle-stimulating hormone glycosylation pattern: impact on oocyte quality and clinical outcome. Fertil and Steril 2010; 94(5):1782-6.
28. Aboulghar M *et al.*, Prospective, randomized study comparing highly purified urinary follicle-stimulating hormone (FSH) and recombinant FSH for *in vitro* fertilization/intracytoplasmic sperm injection in patients with polycystic ovary syndrome. Fertil Steril 2010; 94(6):2332-2334.
29. Murber A *et al.*, Impact of highly purified versus recombinant follicle stimulating hormone on oocyte quality and embryo development in intracytoplasmic sperm injection cycles. Acta Biol Hung. 2011;62(3):255–64.
30. Kemeter P *et al.*, 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;5:1-13.
31. Selman HA *et al.*, Simultaneous administration of human acidic and recombinant less acidic follicle-stimulating hormone for ovarian stimulation improves oocyte and embryo quality, and clinical outcome in patients with repeated IVF failures. Eur Rev Med Pharmacol Sci. 2013;17:1814-9.
32. Gurgan T *et al.*, Sequential (hFSH + recFSH) vs homogenous (hFSH or recFSHalone) stimulation: clinical and biochemical (cumulus cell gene expression) aspects. J Assist Reprod Genet. 2014;31(6):657-65.
33. Colacurci N *et al.*, Sequential protocol with urinary-FSH/recombinant-FSH versus standard protocol with recombinant-FSH in women of advanced age undergoing IVF. Gynecol Endocrinol. 2014;30(10):730–3.
34 Fostimon SmPC

Date of last revision: January 12, 2018