Meriofert®

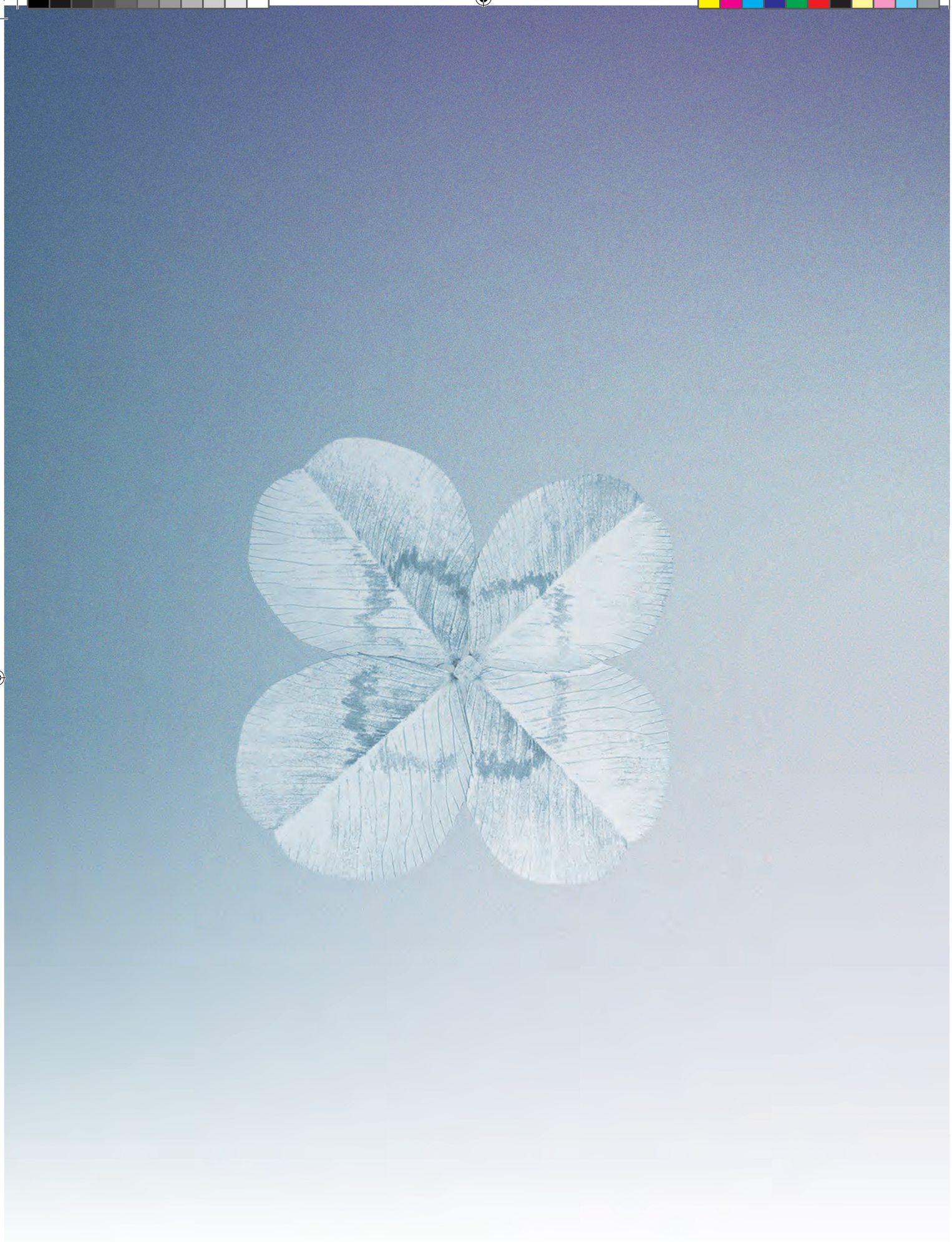
Highly Purified hMG

When Nature meets Innovation

Prescribing information on page 17.

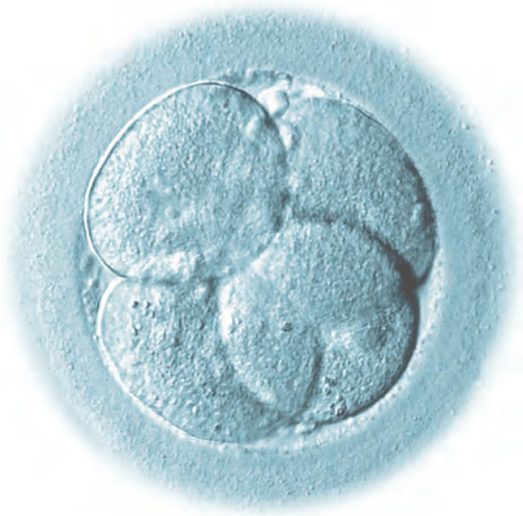
IBSA

Caring Innovation



Meriofert®

Highly Purified hMG



The latest addition to the world of infertility treatments[1-2]

AN ORIGINAL NATURAL FORMULA

Meriofert®'s formula is the first to use highly purified hFSH in concert with highly purified placental hCG sourced from the urine of pregnant women[1-2].

A CHOICE OF EFFICIENCY

Clinical studies show that **Meriofert®** is an efficient and reliable alternative to current marketed hMG preparations, enabling reduced drug consumption and treatment duration while retrieving a higher number of mature oocytes and cleaved embryos[2-3].

A RELIABLE ALLY

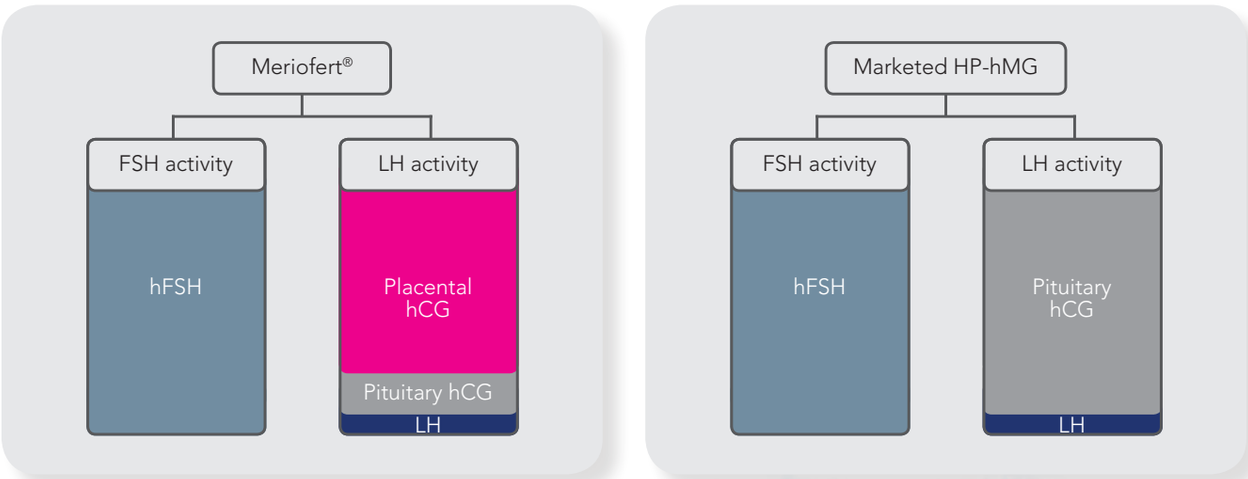
Recognising the crucial role played by the carbohydrate moiety in the FSH and hCG molecules, IBSA designed a natural, chemically non-aggressive purification protocol that manufactures FSH and hCG in parallel processes, effectively preserving balanced glycosylation and ensuring the highest levels of purity and quality[4].

IBSA

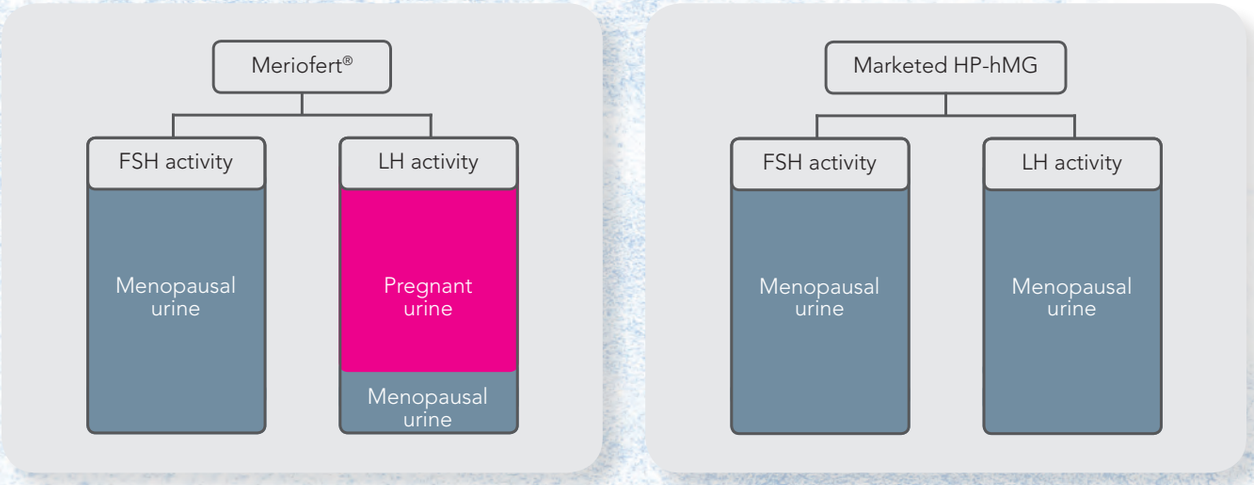
AN ORIGINAL NATURAL FORMULA

Helping nature take its biochemical course

IBSA's new highly purified menotrophin (HP-hMG) preparation **Meriofert®** contains 75 IU (or 150 IU) follicle stimulating hormone (FSH) and luteinising hormone activity (LH/hCG) per vial. Unlike other marketed HP-hMG preparations, in which FSH and LH/hCG (luteinising hormone and human chorionic gonadotrophin) from pituitary origin, both extracted from urine of menopausal women are present[5], **the LH activity promoted by Meriofert® is mainly provided by highly purified hCG of placental origin and is therefore sourced from the urine of pregnant women[1].**



Schematic representation of Meriofert®'s original natural formula and comparison with other marketed HP-hMG
(Adapted from textual data)[1-5]



Scheme of the different sources of gonadotrophins: Meriofert® vs. the market reference
(Adapted from textual data)[1-5]

LH activity in **Meriofert®**

Meriofert®'s LH activity is almost entirely provided by the spiking of placental hCG to the FSH component, maintaining a low contribution of pure LH to the final LH activity. Because the two hormones show quite a similar structure, the LH action may be entirely replaced by hCG, taking advantage of its prolonged half-life *in vivo*[6-7].

STRUCTURE OF THE GLYCOPROTEIN HORMONE FAMILY AND OF hCG

The human chorionic gonadotrophin (hCG) is a member of the glycoprotein hormone (GPH) family that also includes LH, FSH and TSH. All GPHs are heterodimers consisting of a α-subunit (GPHα) and a β-subunit, non-covalently associated. The α-subunit, which contains 92 amino acids with two N-glycosylation sites, is common to all GPHs (Table 1). The β-subunits confer the receptor and biological specificity and display various degrees of homology among the GPHs[8]. The homology between the β-subunits of the hCG and LH is ~ 80%[9].

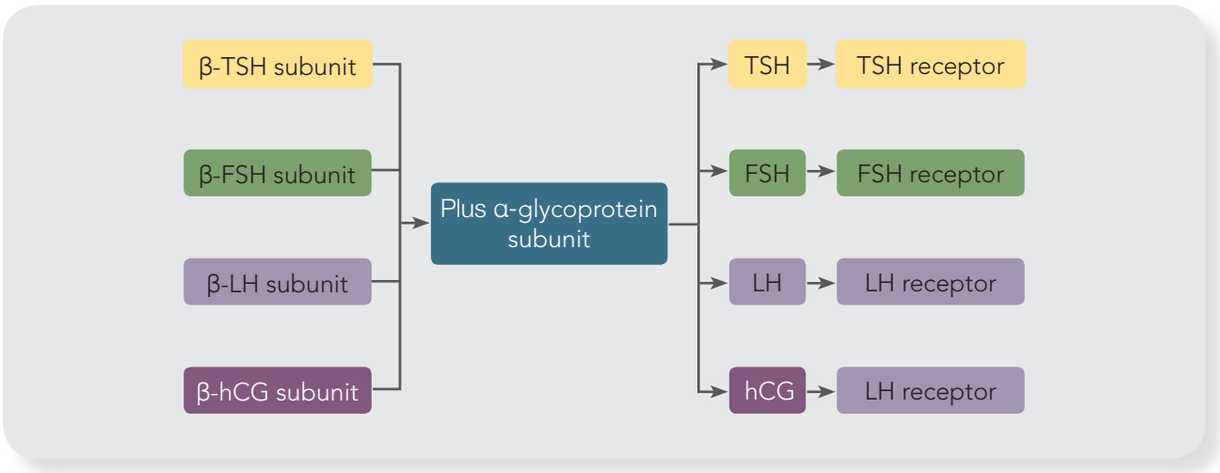


Table 1. The glycoprotein hormone family
hCG and LH glycoproteins bind to the same cellular receptor (LHCGR)[7-8].

The LH activity promoted by Meriofert® is mainly provided by highly purified hCG of placental origin and is therefore sourced from the urine of pregnant women. The hCG fraction of pituitary origin is extracted from menopausal urine.

hCG: a multifaceted molecule

GLYCOSYLATION OF hCG

hCG is a highly glycosylated molecule: 70% of its structure is represented by the peptide, and 30% by carbohydrate residue (oligosaccharides)[8].

The molecule presents 8 different carbohydrate moieties, 6 of which are linked to the β subunit on 2 N- and 4 O- glycosylation sites and 2 linked to α subunit both on an N- glycosylation sites. Owing to variation in the content of terminal sialic acid of its oligosaccharides, hCG displays extensive charge heterogeneity with isoelectric point (pI) values ranging from 3 to 7[8-9].

The secretion, biological activity and half-life *in vivo* of hCG are highly dependent on the glycosylation status of the molecule.

Indeed, the sialic acid content of hCG plays a key role in its receptor binding ability, biological activity and clearance from circulation[8].

Furthermore, the β subunit of hCG shows an amino acid sequence similar to LH, however a notable difference is the presence of a long carboxy-terminal segment containing the four O-linked oligosaccharide residue, **the so called hCG "tail"**. In addition, hCG β-subunits contain two N-linked glycosylation sites, compared with LH's single site[9].

Because of its higher number of both glycosylation sites and sialic acid residues compared with LH, **hCG exhibits a markedly longer half-life *in vivo*** compared to LH[9-10].

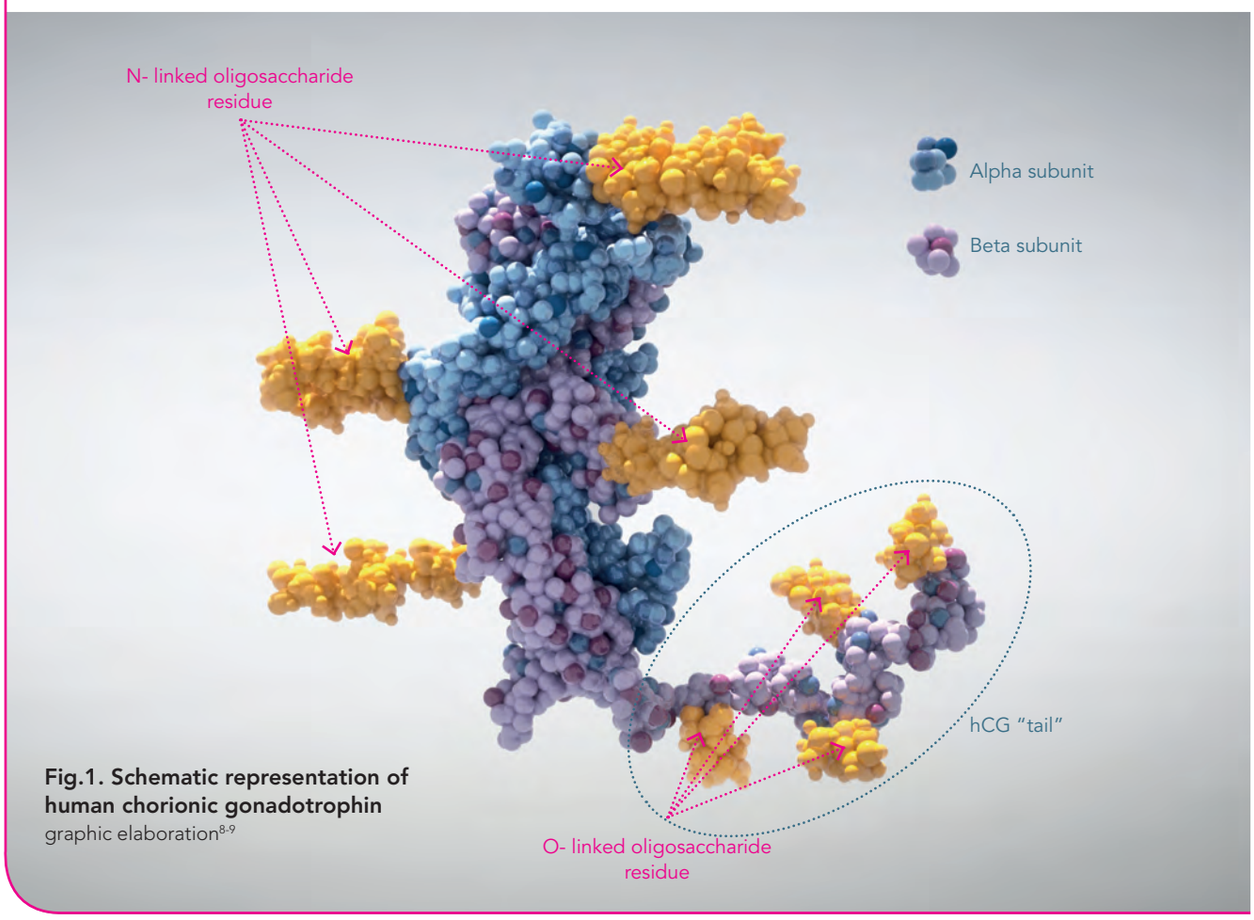


Fig.1. Schematic representation of human chorionic gonadotrophin
graphic elaboration[8-9]

hCG EXISTS IN SEVERAL DIFFERENT BIOLOGICALLY ACTIVE VARIANTS

Once considered as a single molecule, today the term hCG refers to both a family of independent, similarly-structured molecules and a variety of blood and urine breakdown products. Actually, there is a family of hCG variants with identical aminoacid sequences but differing in the glycosylation type and rate produced by different cells that show independent functions[11].

PITUITARY hCG

In women, hCG is produced by the pituitary gland during the menstrual cycle (independently from the pregnancy status) and it controls steroidogenesis and follicular ovulation[10-11].

Typically, the pituitary is able to produce a certain amount of sulfated hCG, thanks to a specific enzyme, GalNac transferase, that binds a terminal sulfate residue on the glycan side-chain instead of the usual sialic acid residue[10].

As a consequence of the sulfonation, the *in vivo* clearance rate of the sulfated hCG is increased in comparison to sialylated hCG (such as the placental hCG) because of the high affinity of liver receptors for the sulfated residue[10].

Previous *in vitro* studies on the characterization of the pituitary hCG (Birken) displayed both a lower biological activity and receptor binding potency of pituitary hCG in comparison to hCG purified from pregnant women (placental hCG)[10].

Consistently, the same authors reported that the sialic acid content of the pituitary hCG is less than that of the placental hCG while the sulfate concentrations are well represented, as shown in table 2:

Table 2. Comparative sulfate content of pituitary and placental hCG subunits (Adapted from Birken)[10]

Protein	Sulfate content (mol/mol)	Sialic acid (mol/mol)
Pituitary hCGα	0.8	1.7
Pituitary hCGβ	2.7	4.6
Placental hCGα	0.4	2.4
Placental hCGβ	0.4	9.4
Placental hCG	0.4	15.6

In general, during the menstrual cycle sulfated hCG levels are lower than circulating LH levels. Conversely the hCG has a higher bioavailability thanks to its longer half-life as compared to LH. As such, the two hormones produced by pituitary gonadotropic cells both have equal activities at the joint LHCG receptors in promoting steroidogenesis, particularly progesterone (luteal phase of menstrual cycle) and androstenedione (follicular phase)[11].

In menopause, with the absence of steroid feedback to the hypothalamus, GnRH pulse becomes maximal. The result is the promotion of vast excesses of LH, hCG and FSH to be produced by gonadotropic cells. **Pituitary sulfated hCG is thereby easily detectable in menopausal women[11].**

LH activity in **Meriofert®**

PLACENTAL hCG

Placental hCG has an essential role in pregnancy and maternal adaptation since it promotes the transformation of cyclic ovary *corpus luteum into gravid corpus luteum* enabling the maintenance of ovarian progesterone, estradiol and estrone secretion during the first six weeks of pregnancy. hCG acts like a superagonist of LH by stimulating corpus luteal cells through the LH/CG receptor (LHCGR), until the steroidogenic activity of the fetal-placental unit compensates the maternal ovarian functions[8].

Placental hCG is mainly constituted by "normally glycosylated" hCG (hCG)[9] and hyperglycosylated hCG (hCG-H): both are detectable in the urine of pregnant women.

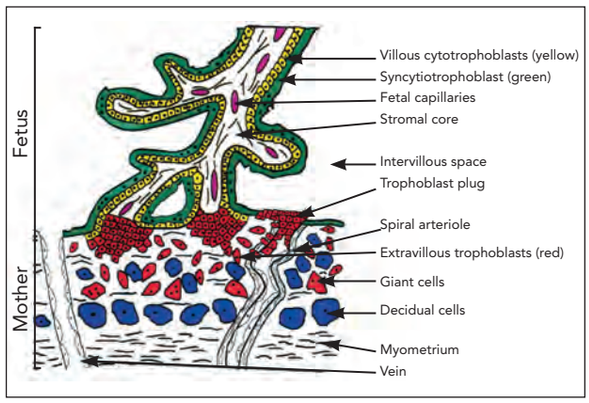


Fig. 2. Representation of a chorionic villus at the implantation site (Adapted from Segond)[12]

The hCG is produced mainly by the syncytiotrophoblast - the epithelial covering of the highly vascular embryonic placental villi - which invades the wall of the uterus to establish nutrient circulation between the embryo and the mother. 99% of it is secreted in maternal blood from week 2 of pregnancy and peaks around 10-12 gestational weeks[8-9] (figure 2).

Hyperglycosylated hCG (hCG-H) is produced in the very early stage of pregnancy. The term "hyperglycosylated" indicates that this form of hCG contains much larger N- and O- linked oligosaccharides[8].

It is produced by invasive extravillus cytotrophoblasts (figure 2) and accounts for 87% of total placental hCG in the 3rd gestational week (GW) and 51% during the 4 GW; the proportion of hCG-H rapidly declines thereafter. The high percentage of hCG-H in early pregnancy is thought to be the driving signal of deep pregnancy implantation[11].

hCG is a multifaceted molecule with different biologically active variants. Pituitary hCG controls steroidogenesis during the menstrual cycle and is typically sulfated[10]. It is highly detectable in menopausal women. Placental hCG is essential for pregnancy maintenance and can be "normally" or "highly" glycosylated (hCG-H) depending on the size of its oligosaccharide residue. It is therefore detectable in pregnant urine only[8-9].

Highly Purified FSH in **Meriofert®**

Similarly to hCG, the follicle-stimulating hormone (FSH) is a member of the GPH family and is thus composed by two non-identical proteic α and β subunits, each having two possible N-linked glycosylation sites (Figure 3) for the oligosaccharide residue chains.

Consequently, FSH is comprised by a family of isohormones or **isoforms** which differ in their ionic charge due to variance in their oligosaccharide structure (carbohydrates) that includes differences in the number of charged terminal sialic acid[13].

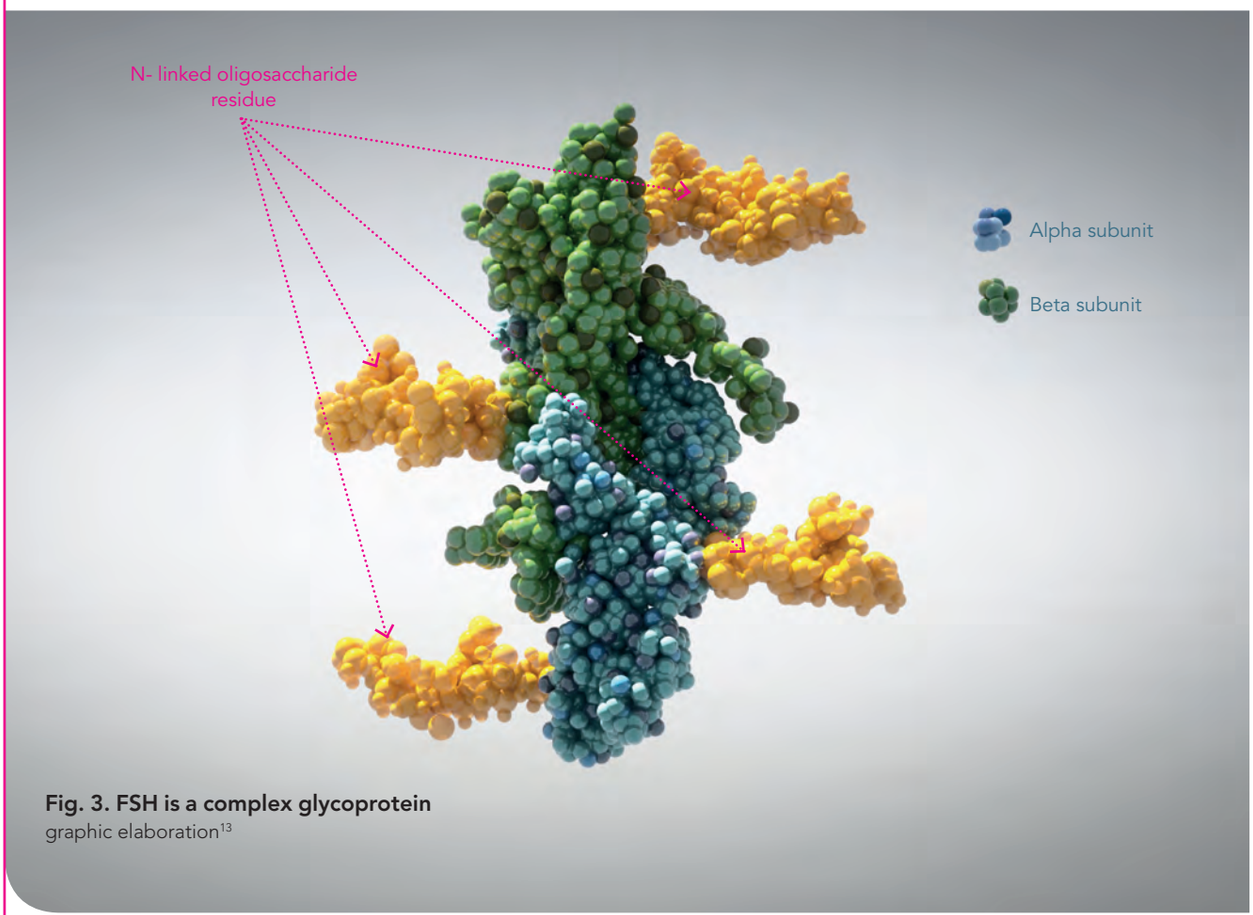


Fig. 3. FSH is a complex glycoprotein
graphic elaboration[13]

The higher the number of carbohydrates branches (or antennae) and of sialic acid residues linked to the proteic backbone of FSH, the higher the acidity of the molecule (Figure 4). Actually, **in humans 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 the heterogeneity of FSH[14].

Highly Purified FSH in **Meriofert®**

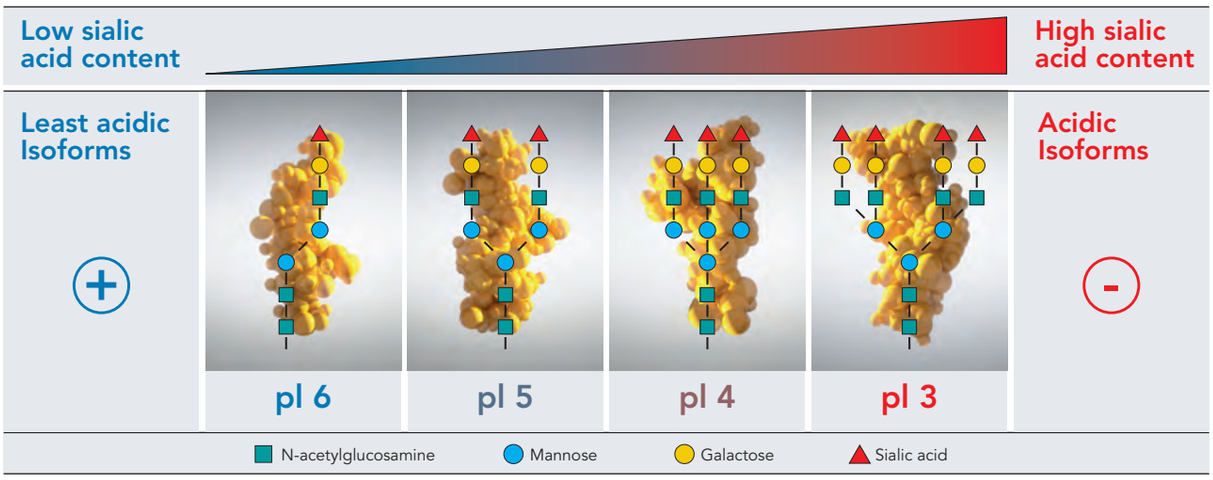


Fig. 4. Schematic representation of the human pituitary range of FSH isoforms according to the isoelectric point (pI) (Adapted from textual data)[14]

IBSA's highly purified FSH contained in Meriofert® was fully characterized in a recent study[4], accurately recording the number of antennae, the composition and the completeness of the glycan moieties present in the FSH active compound.

The results show the prevalence in IBSA's highly purified FSH of more acidic isoforms from species containing greater quantities of sialylated and branched carbohydrate moieties. By contrast, the less acidic isoforms observed for the recombinant glycoproteins contain less sialic acid and a prevalence of diantennary species.

As reported in table 3, the estimated quantitative presence of sialic acid (Z number) resulted the highest for IBSA's highly purified FSH compared to recombinant FSH (recFSH).

Table 3. Oligosaccharide composition and estimated charge number (Z) of IBSA's HP-hFSH and two recombinant preparations (Adapted from Lombardi)[4]

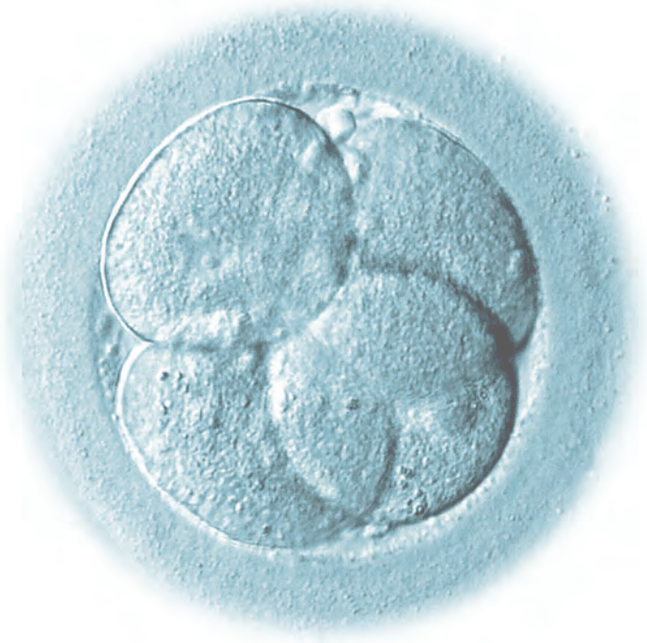
Glycan type	Relative amount %		
	IBSA	recFSH	recFSH
Asialoglycan	2.1	4.6	12.6
Monosialylated	5.1	23.3	43.3
Disialylated	41.6	45.1	33.4
Trisialylated	35.7	19.8	8.6
Tetrasialylated	15.5	7.2	2.0
Estimated Z Number	**257**	**202**	**144**

This study conclusively proves that IBSA's patented protocol, specifically designed to extract FSH from human urine, indeed **preserves the glycosylation status of the molecule throughout every step and minimizes the possible degradation of the oligosaccharide moieties[4].**

FSH is a complex glycoprotein made up by a variety of isoforms with different biological roles. The highly purified FSH fraction contained in Meriofert® is enriched with acidic isoforms thanks to IBSA's exclusive purification protocol, which preserves the natural glycosylation status of the molecules[4].

A CHOICE OF EFFICIENCY

The confidence of clinical data



Randomised, controlled clinical studies suggest that Meriofert® is an efficient alternative in the setting of assisted reproduction (ART) as it reduces drug consumption and treatment duration while retrieving more oocytes and cleaved embryos, and may provide additional practical advantages in the management of ART procedures[2-3].

Italian study

A prospective, randomised, investigator-blind, controlled, clinical study on the clinical efficacy and tolerability of two highly purified hMG preparations administered subcutaneously in women undergoing IVF
Alviggi C *et al.* - Clinicaltrials.gov: NCT00335894[2]

OBJECTIVE

The aim of this multicenter, prospective, randomised, investigator-blind, controlled clinical trial was to evaluate the clinical efficacy and tolerability of **Meriofert®*** compared to marketed reference HP-hMG (Menopur-Ferring) when administered to patients undergoing controlled ovarian stimulation (COS) for IVF, with or without ICSI. This was the first-ever truly randomised controlled trial comparing the safety and the clinical efficacy of two highly purified hMG preparations.

** to notice that in this paper **Meriofert®** takes the brand name of Merional HG*

SETTINGS

Three fertility clinics in Italy participated in this randomised trial between March 2006 and May 2008. One hundred fifty-seven patients were randomised in a 1:1 ratio, according to a computer-generated list, in two parallel groups: 78 started COS with **Meriofert®** and 79 with Menopur.
Enrolled patients [mean age 31.8 (3.7) years for **Meriofert®** and 32.6 (2.9) years for Menopur] underwent a standard, long down-regulation protocol using GnRH agonist. In both groups, a starting hMG dose of 225 IU was maintained for the first 4 - 5 days.

RESULTS

Results of the study (Table 4) showed that both highly purified hMG preparations were equivalent in terms of number of oocytes retrieved (primary endpoint: 8.8 ± 3.9vs 8.4 ± 3.8, p = 0.54).
In the patients treated with Meriofert®, a higher occurrence of mature oocytes (78.3% vs 71.4%, p = 0.005) was observed **and a reduced quantity of gonadotrophins administered per cycle** (2,556 ± 636 IU vs 2,969 ± 855 IU, p<0.001). Fertilization, cleavage and implantation rates, number of positive β-hCG (pregnancy) tests, and clinical pregnancy rate were comparable in the two groups. Both treatments were well tolerated.

One limitation of this study was that the oocyte fertilization procedure and embryo transfer had to be performed in compliance with the Italian legislation on assisted reproduction in force at the time of the study (Legge 40/2004); according to this law (later modified by the Italian Supreme Court), no more than 3 oocytes per patient were inseminated and all the available embryos were transferred. No oocytes, 2PN zygotes or embryos were frozen and no embryo was discarded. There was no significant difference in the number of mature oocytes microinjected, and the fertilization and cleavage rates were comparable between the treatment groups. Before transfer, embryos were scored according to the criteria established by Veeck, showing no differences between treatment groups.
The implantation rate per embryo transfer, the positive β-hCG (pregnancy) test and the clinical pregnancy rate were equivalent between treatment groups. The occurrence of relevant complications such as OHSS and miscarriage was similar in patients treated with **Meriofert®** or Menopur.

CONCLUSIONS

The results of this study support the efficacy and safety of **Meriofert®** given subcutaneously for assisted reproduction techniques. **Efficiency of Meriofert® appears to be higher due to the reduced quantity of drug used and the higher yield of mature oocytes retrieved**.
In summary, **Meriofert®** and Menopur were proven to be equally effective in achieving proper outcome of ART. **Meriofert® appears to be more efficient than Menopur in this setting as it reduces drug consumption and treatment duration** and may provide additional practical advantages in the management of ART procedures.

Italian study

	N	Meriofert®	N	Menopur	p value[a]
COS duration (days)	78	11.3 (1.5)	79	12.3 (2.1)	<0.001
hMG units, total	78	2555.8 (635.9)	79	2968.7 (854.8)	<0.001
hMG units, daily	78	224.2 (37.0)	79	238.6 (48.7)	0.04
Ratio MII/Total oocytes retrieved (%)	72	78.3	73	71.4	0.005
Ratio Immature/Total oocytes retrieved (%)	72	20.4	73	26.3	0.01
Nr of inseminated oocytes	72	2.7 (0.7)	73	2.7 (0.7)	0.42
Fertilization rate[a]	70	88.5	72	92.5	0.18
Positive β-hCG test, n		25		27	-
/ OPU, %	72	34.7	73	37.0	0.78
/ transfer, %	67	37.3	72	37.5	0.98
Implantation rate[b] %	67	15.7	72	15.4	0.94
Clinical pregnancies, n		20		20	-
/ OPU, %	72	27.8	73	27.4	0.96
/ transfer, %	67	29.9	72	27.8	0.79
Abortion rate, n (%)		1 (5.0)		2 (10.0)	-

Table 4. Stimulation and fertilization parameters (Adapted from Alviggi)[2]
Note: Where not specified, data are expressed as mean (SD)
[a] Fertilization rate and cleavage rate calculated per inseminated oocyte
[b] Implantation rate defined as the total number of gestational sacs divided by the total number of embryos transferred.

European study

A randomised, controlled trial comparing the efficacy and safety of a new hMG preparation to a reference product in patients undergoing controlled ovarian stimulation for in vitro fertilization.
Lockwood *et al.* - Clinicaltrials.gov: NCT01312766[3]

OBJECTIVE

The aims of this prospective, investigator-blind, randomised, controlled, parallel-group, multicenter study were to confirm the non-inferiority of **Meriofert®** compared to Menopur with regard to clinical outcome (the primary endpoint being the total number of oocytes retrieved), and **to compare the incidence of clinically significant ovarian hyperstimulation syndrome (OHSS) according to Golan Criteria in patients treated with Meriofert® compared to patients treated with Menopur.**

SETTINGS

270 women undergoing in vitro fertilization (IVF) were randomised from March 2011 through April 2013. Women aged 18-40 years (mean age 33.3 (4.0) and 33.0 (4.1) for **Meriofert®** and Menopur respectively), with BMI ≤30 kg/m2 and <3 prior completed assisted reproductive technology (ART) cycles, exhibiting baseline (day 2-3) FSH <10 IU/L and E2 <80pg/ml, undergoing IVF at 6 centers in 5 European countries, were enrolled. Standard long down-regulation with GnRH-agonist was performed before starting COH. After confirmation of down-regulation, patients were randomised to one of the two treatment groups and were instructed on self-administration and supplied with the assigned medication, with the first dose set at 150 IU for patients aged ≤35 years or 225 IU for patients aged >35 years and commenced 0 to 3 days following confirmation of down-regulation.

MAIN RESULTS

Primary endpoint: Total number of oocytes

In the ITT population, **the mean (±SD) number of oocytes retrieved was significantly higher (P <0.05) in women stimulated with Meriofert® (11.6±6.6) than in those stimulated with Menopur (9.7±5.9) (Table 5).** The difference [**Meriofert®**–Menopur] in mean number of oocytes retrieved was +1.9, with a 95% CI of the difference equal +0.43 to +3.43 (i.e. a 95% CI lower limit greater than the predefined clinically significant difference of -2.1). These results were confirmed in the PP analysis, for which the total number of oocytes retrieved was 12.3±6.2 in the **Meriofert®** group and 10.1±5.7 in the Menopur group.

Secondary endpoints:

No statistically significant differences between **Meriofert®** and Menopur were seen for implantation rate and pregnancy outcome parameters: positive serum pregnancy test rate, clinical pregnancy rate, delivery and live birth rate (Figure 5). Although there was no statistically significant difference in the total and mean daily units of hMG used (Table 5), **the duration of the stimulation was shorter in the Meriofert® group. The increased number of oocytes and mature (MII) oocytes retrieved in the Meriofert® group was also associated with an increased number of cleaved embryos obtained** (Table 5). This significantly higher yield obtained with Meriofert translated into a higher number of cryopreserved embryos available for subsequent transfer. The cumulative pregnancy rates were 46% (n=58/126) and 43% (n=56/129) respectively, for the PP population (Figure 5).

DISCUSSION

The use of **Meriofert®** led to retrieving more oocytes, MII oocytes and cleaved embryos in ART than in a classical hMG reference. **Our results are concordant and confirm the results of a prior study[3] showing that Meriofert® had shorter COS that used less drug while providing a similar oocyte yield.** In this study, with the same quantity of drug and again a shorter stimulation period, significantly more oocytes were retrieved in the **Meriofert®** group.

CONCLUSIONS

The strength of this study resides in the randomised controlled trial which validates its result: more oocytes retrieved with the new hMG preparation. The fact that this difference also translates into more mature oocytes and embryos being obtained suggests that the new hMG preparation may also foster higher cumulative IVF outcome. However the study was not powered for comparing pregnancy rates obtained with the two hMG preparations, thus additional studies should be performed to confirm these findings. **In light of the results obtained in this RCT, Meriofert® is an effective alternative for controlled ovarian stimulation in IVF cycles. As suggested by the National Institute for Clinical Excellence (NICE)[15], the choice of gonadotrophin should depend upon availability, patient convenience and cost-effectiveness. In undertaking this calculation, the total amount of drug needed and the duration of stimulation should be important parameters.**

Variable	Meriofert® (N=135)	Menopur (N=135)	P value*
Total hMG units, Mean (IU)	2171.4 (980.0)	2303.6 (906.4)	NS
COH duration (days)	10.2 (1.3)	10.6 (1.5)	0.02
Oocytes retrieved, total (n)	11.6 (6.6)	9.7 (5.9)	0.012
Mature (Grade III-metaphase II) oocytes (n)	10.3 (6.0)	8.2 (5.1)	0.002
Ratio MII/Total oocytes retrieved (%)	85.0	80.9	0.004
Inseminated-injected oocytes, (IVF + ICSI) (n)	10.8 (5.9)	8.4 (5.0)	<0.001
Cleaved embryos on day 2 (n)	5.8 (3.8)	4.8 (3.7)	0.04
Implantation rate, %	29.1 (41.0)	28.2 (36.9)	NS

Table 5. Stimulation and fertilization parameters (ITT population) (Adapted from Lockwood)[3]
ITT, intention to treat population; n=135 in the Meriofert group; n=135 in the Menopur group
Data are reported as (mean ± SD) if not otherwise specified.
ICSI, intracytoplasmic sperm injection; NS, not statistically significant.
* F-test (analysis of variance) for continuous variables, Fisher's exact test for categorical variables.

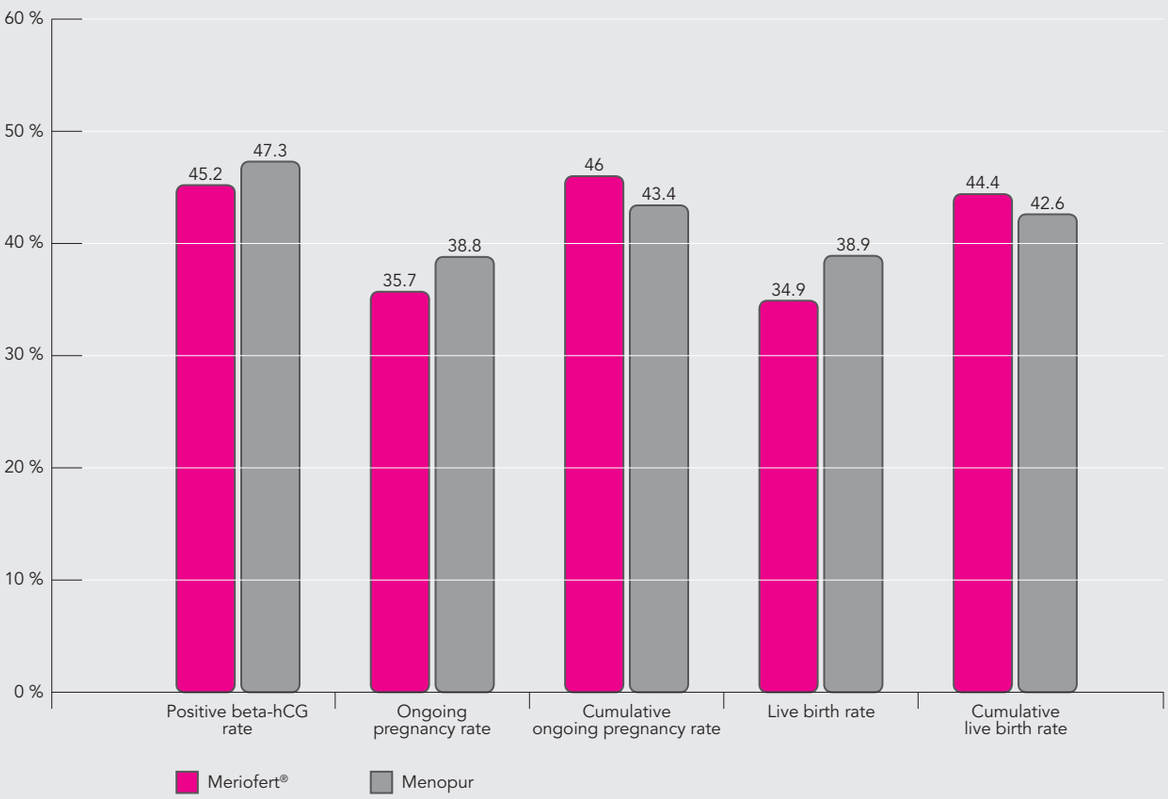
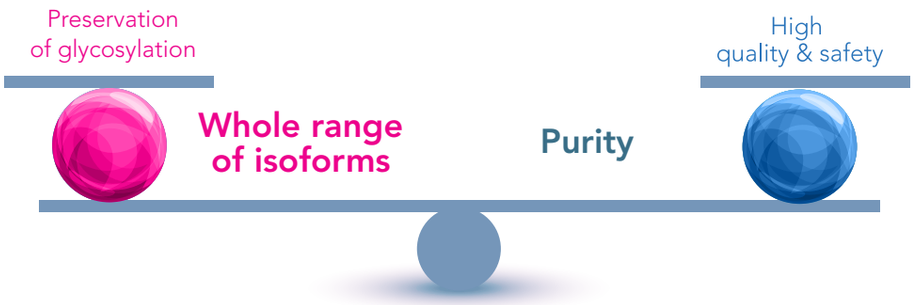


Figure 5. Pregnancy outcomes (PP population) (Adapted from Lockwood)[3]
PP, per protocol population; n=126 in the Meriofert group; n=129 in the Menopur group.
P-value not statistically significant for any of the parameters (Fisher's exact test for categorical variables).

A RELIABLE ALLY IN ART PROGRAMS

The case for unparalleled purity

By recognising the pivotal role of carbohydrate components in both the FSH and hCG molecules, IBSA has designed and patented an innovative, non aggressive purification process that maintains the ideal natural glycosylation balance and reaches the highest levels of purity and quality. Unlike other marketed hMG preparations in which post-menopausal urine is the only manufacturing source, **the Meriofert® starting material is urine collected both from pregnant and post-menopausal women, enabling a parallel, step-by-step purification process that preserves the carbohydrate moieties of the molecule and yields unparalleled purity for both the FSH and hCG components[4-16].**



IBSA PURIFICATION PROCESS

The warranty of a unique global quality

Based on the most advanced technology and know-how of the structure-function of gonadotrophins, IBSA's purification process provides a **benchmark of high quality and safety** for the obtainment of the **highest purity** and **a full range of gonadotrophins molecular species[4].**

IBSA's state-of-the-art, non-aggressive purification process preserves the natural glycosylation balance of its components while guaranteeing unparalleled purity levels[4].

Performed all-in-house under the same global quality assurance system, the process workflow includes:

- Urine collection
- Early purification
- Final purification

STEP 1

URINE COLLECTION AND EARLY PURIFICATION

Urines are collected under IBSA's direct responsibility applying an internationally approved GMP quality system. The initial purification steps were designed to reduce the load of proteins and other small urinary. It includes selective precipitation and solubilisation under mild conditions in order to eliminate some urinary components and to preserve the molecular structure of the FSH and the hCG. This enables avoiding the use of further harsh solvents or chemicals to reach the targeted purity. Early purification also includes some validated virus-cleaning steps which efficiently eliminate or inactivate viruses which could be theoretically present in the initial urines.

STEP 2

FINAL PURIFICATION

The final purification steps include a series of chromatographies which enable recovery of the whole range of the FSH and hCG isoforms, eliminating the urinary impurities.

In particular, the **Blue Sepharose chromatography is performed on an affinity resin, based on a patented, innovative concept that** allows high selectivity in separating the different protein species and extended recovery of all the natural species, **thus resulting in an extremely highly purified product (Figure 6).**

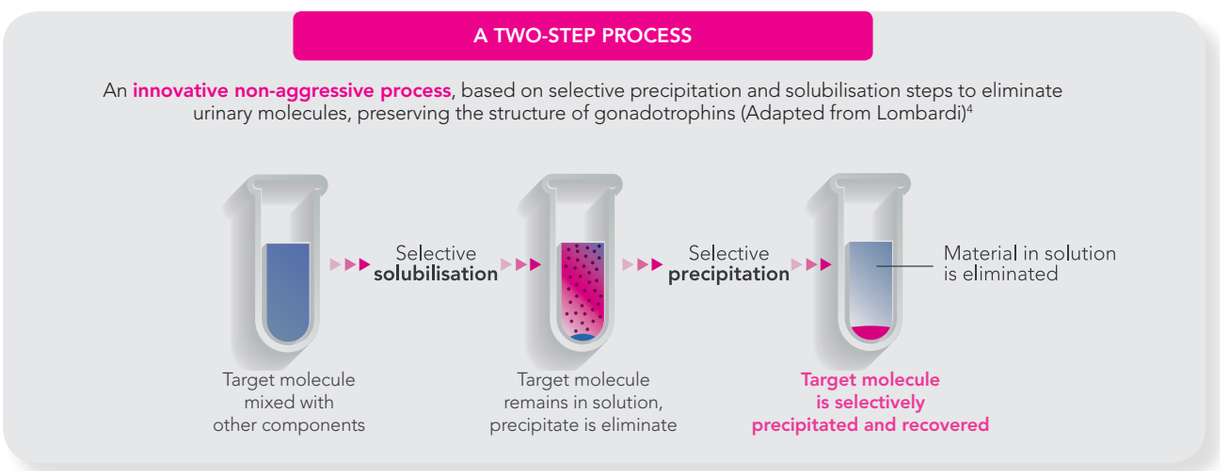


Fig. 6. Schematic representation of the main steps of IBSA's purification process

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