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The Gonadotropins FSH and LH and their use in Adult Women – an Overview*

Joint Statement by the German Society for Gynecological Endocrinology and Reproductive Medicine (DGGEF) and the German Professional Association of Gynecologists (BVF)

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The glycoprotein hormones LH and FSH are essential for reproduction. They consist of two polypeptide units. The alpha unit has 92 amino acids and is virtually identical for FSH, LH, thyroid-stimulating hormone (TSH) and human chorionic gonadotropin (hCG). The secretion in the anterior pituitary gland underlies neuroendocrine control of the hypothalamic-pituitary-gonadal axis. Depending on the level of maturity of the follicle and on the phase of the menstrual cycle LH and FSH regulate the steroidogenesis in theca- and granulosa cells of the ovary.

The pregnancy hormone hCG is produced by Langerhans cells in the syncytiotrophoblast of the placenta. It is very similar to LH in structure and binds to the LH receptor, but with a half-life of 36 h has a longer effect in duration. hCG administration can replace the LH peak in the middle of the ovarian cycle and helps to improve luteal function. However, it cannot prevent regression of the corpus luteum.

For more than 30 years gonadotropins have been crucial elements of pharmacological ovarian stimulation in assisted reproductive techniques (ART) in primary and secondary infertility and the treatment of hypogonadotropic hypogonadism. First menotropins have been extracted from the urine of postmenopausal women. The application of recombinant DNA technology has resulted in the development of recombinant FSH.

Further aims have been to avoid daily injections by modifying the FSH molecule.

Compounds available at present:

- Highly purified human-derived follicle-stimulating hormone: Bravelle® (Ferring)
- Recombinant-DNA products:
 - Follitropin alpha: Gonal-F® (Merck-Serono)
 - rec. FSH: Follitropin beta: Puregon® (MSD)
 - long acting rec. FSH: Corifollitropin alpha: Elonva® (MSD)
 - rec. hLH: Lutropin alpha: Luveris® (Merck Serono)
- Compounds with more than one active agent:
 - human urinary-derived preparations: hMG HP: FSH, LH, hCG = 75 IU LH: Menogon HP® (Ferring)
 - recombinant fixed-dose combinations: 150 IE rec-hFSH / 75 IU rec-hLH Pergoveris® (Merck Serono)

Dosing: FSH and hMG preparations can be dosed equally and are applicable for single use or may be combined with each other. This also applies to recombinant fixed-dose combinations and long-acting FSH preparations. The dosage always must be adapted to the age, AFC (antral follicle count) and AMH (Anti müllerian hormone) of the individual patient. From day 3 to 9 of the menstrual cycle up to 100 IU of FSH might be injected daily for timed intercourse or intrauterine inseminations and up to 300 IU for IVF/ICSI.

In order to achieve a successful outcome of ART it is also important to choose a suitable stimulation regimen. There are protocols for controlled ovarian hyperstimulation using GnRH agonists (long protocol, short protocol, ultra-short protocol, ultra-long protocol) or GnRH antagonists as adjuvant therapy.

Step-up-protocols: In a step-up regimen patients start with a lower dosage in order to avoid hyperresponse of the ovaries. The dosage as well as the intervals can be adjusted individually during stimulation.

Step-down-protocols: In order to achieve a maximum amount of recruited follicles in a step-down protocol patients start with a higher dosage and then decrease the dosage step by step in order to avoid hyperstimulation.

In the long GnRH agonist protocol (long protocol, GnRHa long) GnRHa treatment is initiated in the mid-luteal phase of the preceding cycle at least 10–14 days before stimulation with gonadotropins starts. The protocol allows both physicians and patients to schedule the start of stimulation according to their needs. However, for potential high-responder patients there are limited possibilities to avoid ovarian hyperstimulation syndrome. According to the annual report of the German IVF Register (D.I.R.) the long-protocol was the second most used regimen in Germany in 2013. It has been used in 27.2% (2402 of 8824) IVF cycles and 28.6 % (8784 of 30710) ICSI cycles.

In the short protocol the agonist is initiated in the early follicular phase (day 1 to 3 of the cycle).

In the ultra-short protocol, a shorter period of GnRH-a administration for 3 days is chosen. The short GnRH protocols have been used in 6.5% of all ICSI cycles and 7.6% of all IVF cycles in Germany in 2013.

The ultra-long-protocol uses ovarian suppression for up to 6 months as a recognized treatment of endometriosis prior to the administration of gonadotropins. Stimulation starts 14 days after the last monthly injection of GnRHa and is similar to the long protocol.



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GnRH-antagonist protocols are frequently used in women who are low-responders to ovarian stimulation or potential high-responders. The GnRH antagonist is usually initiated on the 6th day of FSH administration or when the dominant follicle has a diameter of at least 12 mm. Triggering ovulation using GnRH agonists instead of hCG can prevent severe ovarian hyperstimulation syndrome (OHSS). Because of impaired luteal function and in high-risk patients it seems prudent to freeze all embryos for future transfer. In 2013 the GnRH-antagonist protocol was the most commonly used protocol according to the DIR annual report. It has been used in 55.7% (4914 of 8824) IVF cycles and 55.6% (17,080 of 30,710) ICSI cycles.

New IVF protocols using less gonadotropins and an GnRH antagonist starting at the stage of a dominant follicle (modified natural cycle) or no gonadotropins at all (natural cycle IVF) have also been established. To date there is no reported benefit as far as life-birth-rates are concerned compared to conventional protocols.

Ovarian hyperstimulation: Iatrogenic hyperstimulation and induction of ovulation with hCG can result in activation of the ovarian renin angiotensin system leading to symptoms of ovarian hyperstimulation syndrome (OHSS). To date there are no consistent standards of treatment. Consensus over an interdisciplinary approach yet has to be achieved.

Future aspects: At present biosimilars are also available. New FSH molecules are subject of current research. Pharmacokinetics and Pharmacodynamics of different substances vary to a great extent, oral effective GnRH antagonists, oral effective gonadotropins. **J Reproduktionsmed Endokrinol_Online 2015; 12 (4): 360–76.**

Key words: gonadotropins, new FSH-molecules, modified natural cycle, natural cycle, biosimilars, hCG, ovarian Hyperstimulation (OHSS)

■ Introduction

The glycoprotein hormones Luteinising Hormone (LH) and Follicle Stimulating Hormone (FSH) are essential for human reproduction.

For more than 30 years gonadotropins have been crucial elements of pharmacological ovarian stimulation in assisted reproductive techniques (ART) in primary and secondary infertility and the treatment of hypogonadotropic hypogonadism.

All gonadotropins consist of two polypeptide units. The alpha units of FSH, LH, TSH and hCG are almost identical and consist of 92 subunits. Beta units vary and determine the specific function of the hormone. Sugar chains also vary within species and in FSH and LH may be influenced by estrogenlevels.

■ 1. History of Gonadotropins

As early as 1910, studies with dogs showed that partial ablation of the pituitary resulted in gonadal atrophy [1]. In 1927, Smith and Engle described for the first time how Ovarian function depends on the secretion of gonadotropins in the pituitary gland [2]. Also in 1927, the gynecologists Selmar Aschheim and Bernhard Zondek detected gonadotropins in the urine of pregnant women for the first time. By injecting them into immature mice they discovered maturation of follicles, luteinisation and haemorrhage. The bioassay is known as the Aschheim-Zondek test for pregnancy (A-Z test). In 1930, Pregnant Mares Serum Gonadotropin (PMSG) [3] could be extracted from the urine of pregnant mares and pu-

rified. Pharmaceutical preparations used successfully for triggering ovulation in animals and humans became available. In 1939, the first international standard for hCG was introduced under the auspices of the League of Nations, 1940, the Purified urinary preparations of hCG became available [4], in 1941 the concept of a two-step protocol of ovarian stimulation was introduced.

1943 showed a work by Seegar-Jones that gonadotropin was produced *in vitro* in placental tissue culture. 1945 a 5 years' results of sequential and cyclic administration of PMSG and hCG, so called one-two cyclic gonadotropic therapy, followed. PMSG later had to be withdrawn from the market as a consequence of provoking antibody formation. However, animal gonadotropins under the trade name Folistiman (VEB Arzneimittelwerk, Dresden) were still available in some East European countries until 1998.

In 1958 Carl Gemzell extracted gonadotropins from human pituitary glands (hPG). Between 1958 and 1988 hPG was successfully used for ovulation induction [5]. In 1960 Lunenfeld et al reported the first successful induction of ovulation with hMG and hCG followed by pregnancies in hypogonadotropic anovulatory women (Fig. 1) [6].

For an overview over sources and characteristics of different gonadotropins see Table 1.

■ 2. Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH)

The secretion of FSH and LH in the anterior pituitary gland underlies neuroendo-

crine control of the hypothalamic-pituitary-gonadal axis. Depending on the level of maturity of the follicle and on the phase of the menstrual cycle LH and FSH regulate the steroidogenesis in theca- and granulosa cells of the ovary (Fig. 2, 3).

FSH has a Beta subunit of 111 amino acids and a sugar portion which is covalently bonded to asparagine and composed of N-acetylamine, N-acetylglucosamine, galactose and sialic acid. The latter is responsible for the biological half-life.

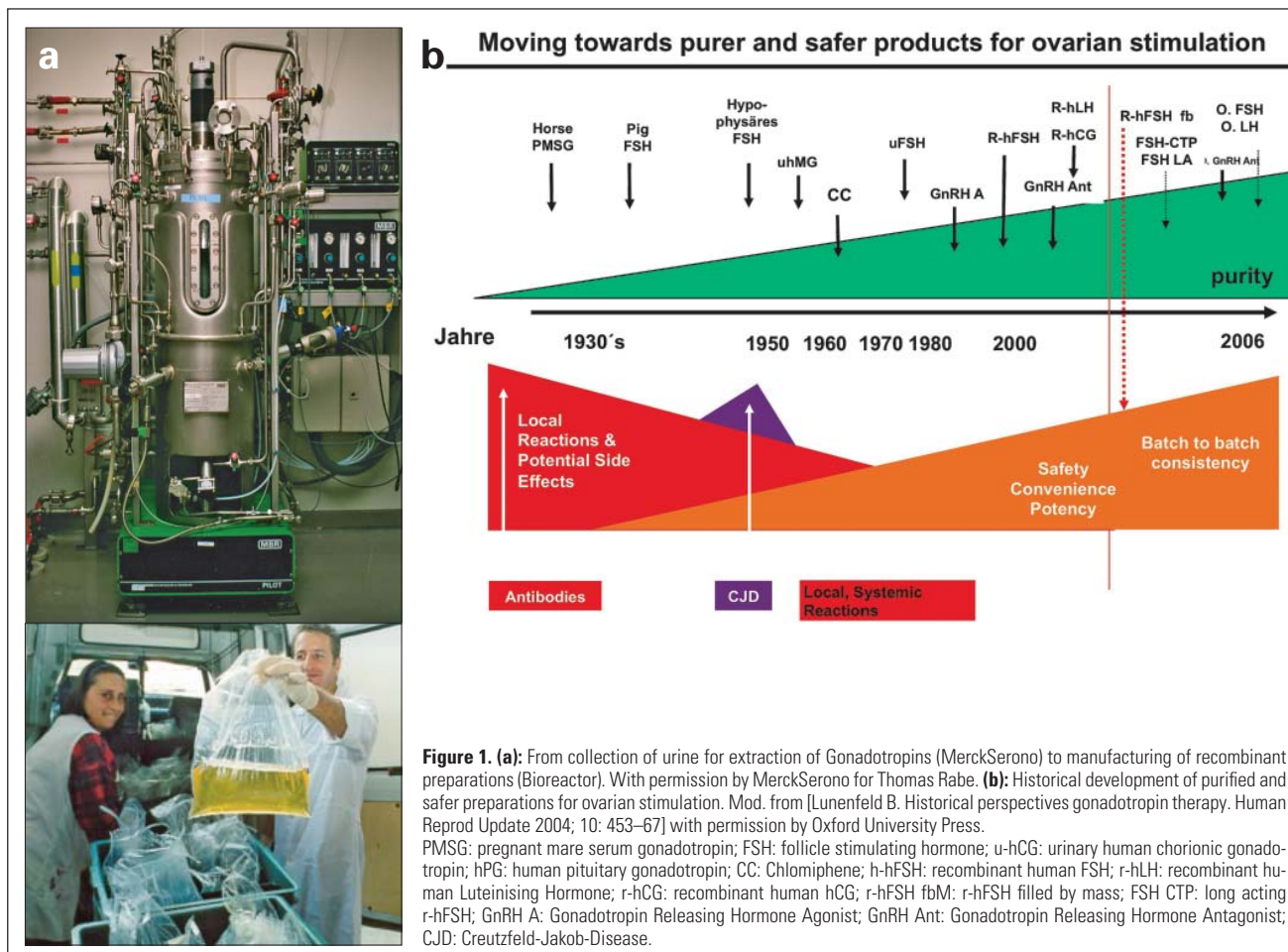
Physiology: FSH is responsible for the development and maturation of follicles. Its main task is the stimulation of estrogen synthesis in ovarian granulosa cells. It binds to specific transmembrane FSH receptors. FSH induces transcription of its own receptors as well as LH and Prostaglandin receptors.

Compounds available at present: See Table 2.

2.1. Urinary Gonadotropins

2.1.1. Human Menopausal Gonadotropin (hMG)

Human menopausal gonadotropin is derived from urine of postmenopausal women, originally obtained from a single nunnery in Italy. It contains the three gonadotropins FSH, LH and hCG. The clinical use began in the 1950s, clinical trials started in the 1960s. Initially the protein content was 97%, urine is now collected in numerous centers in a wide variety of countries. Extraneous urinary proteins are still present in current hMG products. Improved purification techniques resulted in standardization of FSH and LH activity to 75 IU. It may



still contain varying amounts of FSH, LH and hCG. The sugar chain may not be identical to endogenous gonadotropins, due to altered estrogen levels in postmenopausal women.

2.1.2. Urinary FSH

Highly purified (HP) urinary FSH is manufactured by the use of monoclonal antibodies specific to FSH. HP uFSH preparations contain < 0.1 IU LH and the specific activity of FSH is 10,000 IU/mg protein. It contains < 5% unidentified urinary proteins. In HP products batch to batch variation is improved compared to former urinary FSH preparations. However, up to 23% contaminants are possible [7].

2.2. Recombinant Gonadotropin Preparations

Since 1996 recombinant gonadotropins are available. Recombinant preparations for FSH and LH are produced by inserting the genes encoding for the alpha and beta subunits into expression vectors which are transfected into Chinese hamster ovary (CHO) cell lines. The highly effective purification process yields an

FSH preparation with a specific activity > 10,000 IU FSH/mg proteins. Recombinant DNA technology is also considered to be safer and better as far as impurities and the risks of contaminants are concerned. However, there still might remain a slight risk.

uFSH and rFSH have been developed on the presumption that the LH component in urinary hMG might have an adverse impact on folliculogenesis, oocyte quality and embryonic implantation in certain patients.

2.2.1. LH (Luteinizing hormone)

LH has a beta unit of 120 amino acids. LH is essential for estradiol synthesis and follicular development. It is known that a minimum LH secretion is necessary in order to allow stimulation with FSH to succeed. Minimum threshold levels of LH may vary individually as well as the bioactivity of the endogenously produced LH. LH may be added according to the endogenous LH activity [8]. In studies, hypogonadotropic patients with endogenous LH levels < 1.2 IU/l

where proven to be in need of LH supplementation in addition to FSH.

Recombinant LH (rLH) might be a helpful alternative to prevent the risk of OHSS. Dose dependent studies are required to further evaluate the interest of rLH administration as luteal support.

rLH allows to adjust dosing precisely without the risk of LH overexposure. Recombinant LH is available for single use as Lutropin alpha (Luveris®) see Figure 4 containing 75 IU rLH or in recombinant fixed dose combinations (Pergoveris®) containing 150 IU rec.-hFSH and 75 IU rec.-hLH.

2.2.2. Recombinant FSH (Follicle stimulating Hormone)

Recombinant FSH is available as Folliotropin alpha (Gonal f), Folliotropin Beta (Puregon) and long-acting Corifolliotropin alpha (Elonva) (see Fig. 4).

The posttranslational glycosylation process and purification procedures of the two recombinant FSH preparations are

Table 1. Comparison of different Gonadotropins. © Thomas Rabe

	Pregnant mares serum gonadotropin mares	Human pituitary gonadotropin	Menotropins	Highly purified urinary FSH	Follitropin (FSH)	Lutropin (LH)	Corifollitropin	Chorionic gonadotropin	Chorionic gonadotropin
		human	human	human	recombinant	recombinant	recombinant		
Source	Blood of pregnant mares	Human pituitary glands	Urine of postmenopausal women	Urine of postmenopausal women	Transfected CHO cells	Transfected CHO cells	Transfected CHO cells	Urine of pregnant women	Transfected CHO cells
Abbreviation	PMMSG	hPG	hMG	uFSH	r-hFSH	r-hLH	r-hFSH	hCG	r-hCG
Clinical relevance	none	none	available	available	sugarchain	available	available	available	available
Problems	animal	Supply could not meet demand	human		sugarchain	sugarchain	sugarchain	human	sugarchain
	Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women	Contains extraneous urinary proteins, molecule might be altered due to different estrogen levels in postmenopausal women, LH activity mainly derived from hCG	Contains extraneous urinary proteins, molecule might be altered due to different estrogen levels in postmenopausal women, LH activity mainly derived from hCG	Contains extraneous urinary proteins, molecule might be altered due to different estrogen levels in postmenopausal women	Recombinant, not necessarily identical to natural FSH	Recombinant, not necessarily identical to natural FSH	Recombinant, not necessarily identical to natural FSH	Contains extraneous urinary proteins, molecule might be altered due to different estrogen levels in postmenopausal women	Recombinant, not necessarily identical to natural FSH
Side-effects	antibodies	see above	refer to SMPC	refer to SMPC	refer to SMPC	refer to SMPC	refer to SMPC	refer to SMPC	refer to SMPC
Contraindications		1. Tumors of the pituitary or hypothalamic glands 2. Hypersensitivity to the active substance or any of the excipients 3. Ovarian, uterine or mammary carcinoma - Pregnancy and lactation 4. Gynaecological haemorrhage of unknown aetiology 5. Ovarian cysts or enlarged ovaries not due to polycystic ovarian disease 6. Primary ovarian failure 7. Malformation of sexual organs incompatible with pregnancy 8. Fibroid tumors of the uterus incompatible with pregnancy 9. Structural abnormalities in which a satisfactory outcome cannot be expected, for example, tubal occlusion (unless superovulation is to be induced for IVF), ovarian dysgenesis, absent uterus or premature menopause.	1. Tumors of the pituitary or hypothalamic glands 2. Hypersensitivity to the active substance or any of the excipients 3. Ovarian, uterine or mammary carcinoma - Pregnancy and lactation 4. Gynaecological haemorrhage of unknown aetiology 5. 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Sex hormone dependent tumors of the reproductive tract and accessory organs 8. Pregnancy	1. Prior hypersensitivity to recombinant FSH preparations or one of their excipients 2. Primary ovarian failure 3. Uncontrolled thyroid or adrenal dysfunction 4. An uncontrolled organic intracranial lesion such as a pituitary tumor 5. Abnormal uterine bleeding of undetermined origin (see: Selection of Patients) 6. Ovarian cyst or enlargement of undetermined origin (see: Selection of Patients) 7. Sex hormone dependent tumors of the reproductive tract and accessory organs 8. Pregnancy	1. Tumors of the ovary, breast, uterus, pituitary or hypothalamus 2. Abnormal (not menstrual) vaginal bleeding without a known/diagnosed cause 3. Primary ovarian failure 4. Ovarian cysts or enlarged ovaries 5. A history of Ovarian Hyperstimulation Syndrome (OHS) 6. A previous COS cycle that resulted in more than 30 follicles > 11 mm measured by ultrasound examination 7. A basal antral follicle count > 20 8. Fibroid tumors of the uterus incompatible with pregnancy 9. Malformations of the reproductive organs incompatible with pregnancy 10. Pregnancy or lactation (see PRECAUTIONS) 11. Polycystic ovarian syndrome (PCOS) 12. Hypersensitivity to the active substance or to any of the excipients	1. Hypersensitivity to human gonadotropins active substance or to any of the excipients listed in section 6.1. 2. Presence of untreated non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) 3. Breast, uterine, ovarian tumors 4. Gynaecological haemorrhages of unknown aetiology 5. Ovarian, uterine or mammary carcinoma 6. Known or suspected androgen-dependent tumors such as testicular tumors, carcinoma of the prostate or mammary carcinoma 7. Active thrombo-embolic disorders 8. Primary ovarian failure 9. Malformations of sexual organs incompatible with pregnancy 10. Fibroid tumors of the uterus incompatible with pregnancy 11. Postmenopausal women	1. Hypersensitivity to human gonadotropins active substance or to any of the excipients listed in section 6.1. 2. Presence of untreated non-gonadal endocrinopathies (e.g. thyroid, adrenal or pituitary disorders) 3. Breast, uterine, ovarian tumors 4. Gynaecological haemorrhages of unknown aetiology 5. Ovarian, uterine or mammary carcinoma 6. Known or suspected androgen-dependent tumors such as testicular tumors, carcinoma of the prostate or mammary carcinoma 7. Active thrombo-embolic disorders 8. Primary ovarian failure 9. Malformations of sexual organs incompatible with pregnancy 10. Fibroid tumors of the uterus incompatible with pregnancy 11. Postmenopausal women

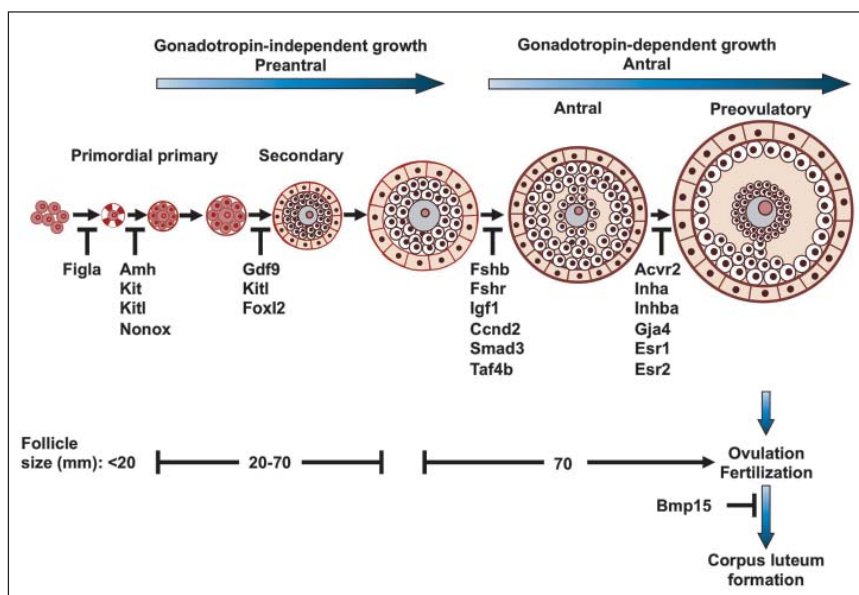


Figure 2. Folliculogenesis. © Thomas Rabe

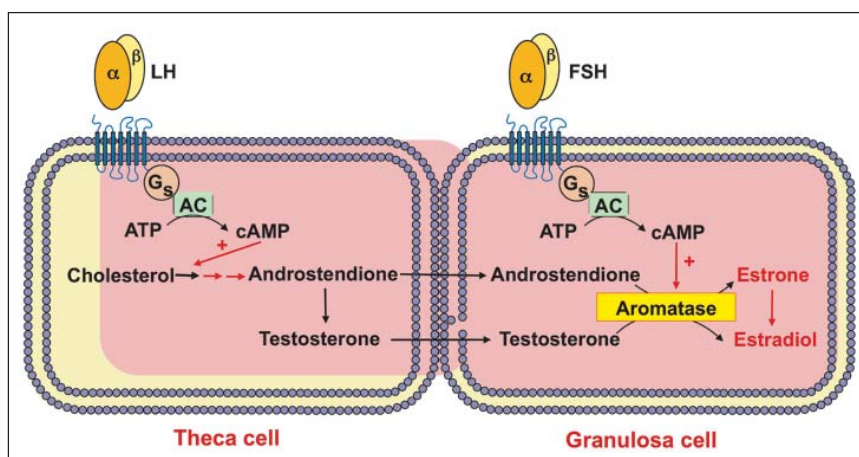


Figure 3. Two cell theory of estrogen production in the ovaries and mechanisms of LH- and FSH-Stimulation. © Thomas Rabe.

different. Thus sialic acid residue compositions and isoelectric coefficients are different [9]. However, there are no proven differences in clinical performance caused by the subtle differences in structure. Due to their high level of purity formulations of both follitropin alpha and

beta are available based on filled by mass method. When filled by mass with follitropin alpha a high consistency in dosing with a variability of only $\pm 2\%$ can be achieved as opposed to a variability of ± 5 to -20% in gonadotropins filled by bioassay [10].

Figures 5 and 6 show the drug design of gonadotropins with a prolonged duration of action. A hybrid beta-subunit containing 28 additional amino acids accounts for the prolonged plasma half-life of 65 hours. A single injection of corifollitropin alfa, thus can replace daily FSH injections for 5 to 7 days.

2.3. Exemplary Summary of Product Characteristics (SMPC) for Follitropin alpha (300 IU, 450 IU, 900 IU) 04/14

2.3.1. Indications

Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate. Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as *in vitro* fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer. FSH in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/l.

2.3.2. Contraindications

- Hypersensitivity to the active substance or to any of its excipients
- Tumors of the hypothalamus or pituitary gland
- Ovarian enlargement or ovarian cyst not due to polycystic ovarian syndrome
- Gynaecological haemorrhages of unknown aetiology
- Ovarian, uterine or mammary carcinoma
- It must not be used when an effective response cannot be obtained, such as
 - primary ovarian failure



Figure 4. Prefilled peninjections with Gonadotropins: Otrivelle, Gonal-[®], Luveris pen for injection (MerckSerono); Elonva: prefilled syringe with Gonadotropin alfa; Puregon-Pen (MSD). Figures provided by MerckSerono and MSD.

Table 2. Gonadotropins (overview of preparations). © Thomas Rabe

Substance	Brand name (company)	Preparation	Dose	Approved therapeutic indications
LH Lutropin alpha	Luveris® (Merck Serono)	Powder and solvent for solution for parenteral injection. Each vial with dry substance contains Lutropin alpha 75 IU	In association with FSH	Luveris in association with a Follicle Stimulating Hormone (FSH) preparation is recommended for the stimulation of follicular development in adult women with severe Luteinising Hormone (LH) and FSH deficiency with an endogenous serum LH level < 1.2 IU
hMG	Menogon® HP Menopur® (Ferring pharmaceuticals)	Powder and solvent for solution for parenteral injection. Each vial with dry substance contains: Menotropin (hMG) 75 IU FSH and 75 IU LH, highly purified.	75–300 IU/day	Treatment of female and male infertility in the following groups of patients: – Anovulatory women: hMG can be used to stimulate follicle development in amenorrhoeic patients. Clomiphene (or a similar ovulation inducing agent which influences steroid feed-back mechanisms) is the preferred treatment for women with a variety of menstrual cycle disturbances, including luteal phase insufficiency with anovulatory cycles and with normal prolactin, and also amenorrhoeic patients with evidence of endogenous oestrogen production but normal prolactin and normal gonadotropin levels. Non-responders may then be selected for menotropin therapy. – Women undergoing superovulation within a medically assisted fertilisation programme: hMG can be used to induce multiple follicular development in patients undergoing an assisted conception technique such as <i>in vitro</i> fertilisation (IVF/ICSI). – Hypogonadotrophic hypogonadism in men: hMG may be given in combination with human chorionic gonadotropin (e.g. Choragon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive.
FSH (urinary) (Urofollitropin)	Bravelle® 75 IU (Ferring pharmaceuticals)	Each vial with dry substance contains: Urofollitropin 82.5 IU equals 75 IU FSH	75–300 IU/day subcutaneously	Anovulation (including polycystic ovarian disease [PCOD] in women who have been unresponsive to treatment with clomiphene citrate.) Controlled ovarian hyperstimulation to induce the development of multiple follicles for assisted reproductive technologies (ART) (e.g. <i>in vitro</i> fertilisation/embryo transfer IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).
Corifollitropin alpha	Elonva® 100 µg/150 µg (MSD)	Solution for injection. Each pre-filled syringe (0.5 ml) contains Corifollitropin alpha 100 µg/150 µg	< 60 kg 100 µg/> 60 kg 150 µg single dose subcutaneously	Controlled Ovarian Stimulation (COS) in combination with a Gonadotropin Releasing Hormone (GnRH) antagonist for the development of multiple follicles in women participating in an Assisted Reproductive Technology (ART) programme.
FSH (recombinant) Follitropin beta	Puregon® 50 IU/0.5 ml/ 300 IU/0.36 ml/600 IU/ 0.72 ml/900 IU/1.08 ml solution for injection (MSD) Puregon® 50 IU/0.5 ml solution for injection (MSD) Puregon® 300 IU/0.36 ml/ 600 IU/0.72 ml/900 IU/ 1.08 ml solution for injection (MSD)	Solution for injection in cartridges: 300 IU in 0.36 ml; 600 IU in 0.72 ml; 900 IU in 1.08 ml aqueous solution for use in Puregon Pen®	50–300 IU/day subcutaneously	In adult females: Puregon is indicated for the treatment of female infertility in the following clinical situations: – Anovulation (including polycystic ovarian syndrome, PCOS) in women who have been unresponsive to treatment with clomiphene citrate. – Controlled ovarian hyperstimulation to induce the development of multiple follicles in medically assisted reproduction programs (e.g. <i>in vitro</i> fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)). In adult males: Deficient spermatogenesis due to hypogonadotrophic hypogonadism.
FSH (recombinant) Follitropin alpha	Gonal-F® 75 IU (5.5 µg) Gonal-F® 450 IU/0.75 ml (33 µg/0.75 ml) Gonal-F® 1050 IU/ 1.75 ml (77 µg/1.75 ml) powder and solution for use in multi-dose vial Gonal-F® 300 IU/0.5 ml (22 µg/0.5 ml)/450 IU/ 0.75 ml (33 µg/0.75 ml)/ 900 IU/1.5 ml (66 µg/ 1.5 ml) solution for injection in pre-filled pen Follitropin alpha (r-hFSH): 300–900 IU/ml	Each multidose vial contains 5.5; 33; 87 µg of follitropin alpha* (equivalent to 75; 600; 1200 IU), in order to deliver 5.5; 33; 77 µg (equivalent to 75; 450; 1050 IU) in 1.75 ml Each ml of the reconstituted solution contains 600 IU Solution for injection in pre-filled pen Follitropin alpha (r-hFSH): 300–900 IU/ml	75–300 IU/day	In adult women: – Anovulation (including polycystic ovarian syndrome) in women who have been unresponsive to treatment with clomiphene citrate. – Stimulation of multifollicular development in women undergoing superovulation for assisted reproductive technologies (ART) such as <i>in vitro</i> fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer. – GONAL-f in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/ml. In adult men: – GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy).
FSH (recombinant) Follitropin alpha Biosimilar	Bemfolia® 75 IU/0.125 ml Bemfolia® 150 IU/0.25 ml Bemfolia® 225 IU/0.375 ml Bemfolia® 300 IU/0.50 ml Bemfolia® 450 IU/0.75 ml solution for injection in pre-filled pen (FINOX) Biotech AG/Schweiz)	Solution for injection in pre-filled pen	75–300 IU/day	In adult women: – Anovulation (including polycystic ovarian disease, PCOD) in women who have been unresponsive to treatment with clomiphene citrate. – Stimulation of multifollicular development in patients undergoing superovulation for assisted reproductive technologies (ART) such as <i>in vitro</i> fertilisation (IVF), gamete intra-fallopian transfer (GIFT) and zygote intra-fallopian transfer (ZIFT). Follitropin alpha in association with a luteinising hormone (LH) preparation is recommended for the stimulation of follicular development in women with severe LH and FSH deficiency. In clinical trials these patients were defined by an endogenous serum LH level < 1.2 IU/ml. In adult men: – Follitropin alpha is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotrophic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy. see above; similar to Bemfolia®
FSH (recombinant) Follitropin alpha Biosimilar	Ovaleap® (Teva) Follitropin alpha 300 IU/0.5 ml	Cartridges for use in pen	75–300 IU/day	

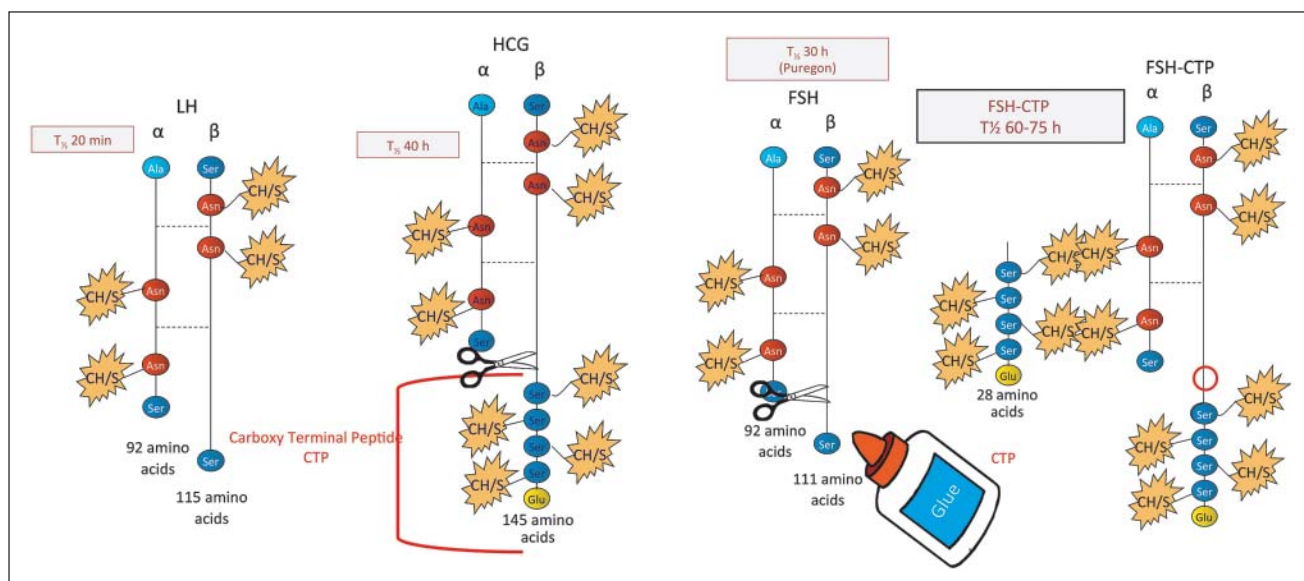


Figure 5. Gonadotropins – Drug design for long-acting Gonadotropins. **Left:** Native structure of LH and hCG with half-life after 20 min and 40 hours. **Right:** Native FSH (left, half-time: 30 hours) and FSH (right) with a prolonged half-life of 60–75 hours after adding 28 AS to the beta-subunit. With permission from G. Griesinger, © 2013.

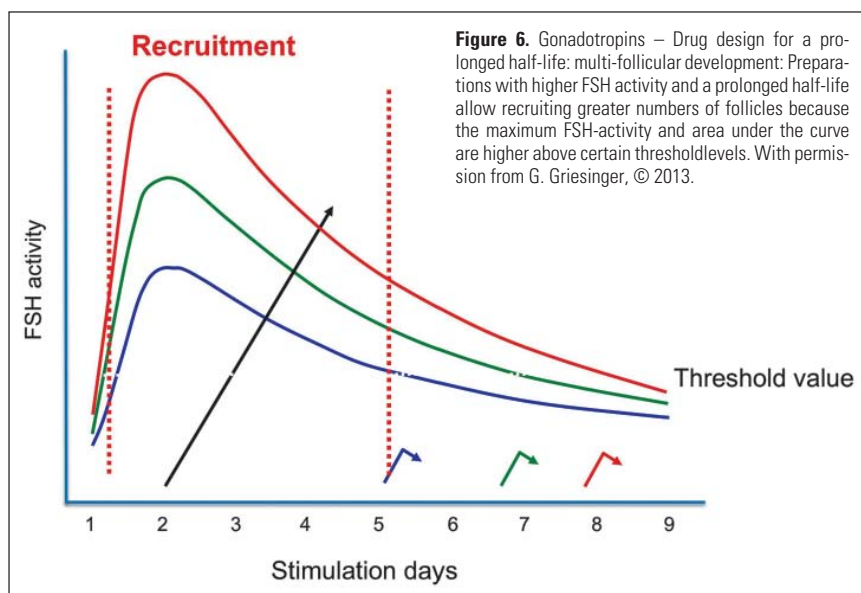


Figure 6. Gonadotropins – Drug design for a prolonged half-life: multi-follicular development: Preparations with higher FSH activity and a prolonged half-life allow recruiting greater numbers of follicles because the maximum FSH-activity and area under the curve are higher above certain threshold levels. With permission from G. Griesinger, © 2013.

- malformations of sexual organs incompatible with pregnancy
- fibroid tumors of the uterus incompatible with pregnancy

2.3.3. Special Warnings and Precautions for Use

The following issues have to be discussed with patients prior to use of gonadotropins:

2.3.3.1. Multiple Pregnancies

According to Hellin's law the natural occurrence of multiples would be as follows: twins 1 in 90 live births (1.05–1.35%), triplets 1 in 8,100 live births (0.01–0.017%). After stimulation with gonadotropins twin birth rates were said

to be 25%, Triplet rates as high as 5 % [11]. By transferring no more than an average of 1.87 embryos in fresh cycles after stimulation with gonadotropins the number of twins was cut back from 1,914 in the year 2012 to 1,487 (22.34%) in 2013; the number of triplets from 61 to 56 (0.84%) [12]. Thus the tendency towards the transfer of a single embryo helps to reduce multiple pregnancy rates. The use of ultrasound monitoring in non-ART treatments (ovulation stimulation medications without ART) also ensures to minimize the risk of multiple pregnancies.

There have been reports of ovarian and other reproductive system neoplasms, both benign and malignant, in women

who have undergone multiple treatment regimens for infertility treatment. It is not yet established whether or not treatment with gonadotropins increases the risk of these tumors in infertile women.

2.3.3.2. Congenital Malformation

The prevalence of congenital malformations after ART may be slightly higher than after spontaneous conceptions. This is thought to be not due to gonadotropins used for stimulation but due to differences in parental characteristics (e.g. maternal age, sperm characteristics) and multiple pregnancies.

2.3.3.3. Thromboembolic Events

In women with recent or ongoing thromboembolic disease or women with generally recognised risk factors for thromboembolic events, such as personal or family history, treatment with gonadotropins may further increase the risk for aggregation or occurrence of such events. In these women, the benefits of gonadotropin administration need to be weighed against the risks. It should be noted however that pregnancy itself as well as OHSS also carry an increased risk of thromboembolic events.

2.3.3.4. Rare Events

The treatment with gonadotropins might enhance growth of preexisting tumors of the hypothalamus or pituitary gland. Safety, efficacy and pharmacokinetics of recombinant FSH in patients with renal or hepatic impairment have not been established. Patients with porphyria or a

Table 3. Comparison of half-life rLH and rhCG. After [le Cotonnec JY, et al. Pharmacokinetic and pharmacodynamic interactions between recombinant human luteinizing hormone and recombinant human follicle-stimulating hormone. *Fertil Steril* 1998; 69: 201–9] and [Trinchard-Lugan I, et al. Pharmacokinetics and pharmacodynamics of recombinant human chorionic gonadotropin. *RBMonline* 2002; 4: 106–15].

Molecule and Dose	rLH 150 IU	rhCG 250 µg
Half-life (initial)	1.0 + 0.2	4.7 + 0.8
Half-life terminal (h) i.v. administration	11 + 8	28 + 3
Half-life terminal (h) s.c. administration	21 – 24	72 – 96

family history of porphyria should be closely monitored during treatment with rec-FSH. Deterioration or a first appearance of this condition may require cessation of treatment.

■ 3. Human Chorionic Gonadotropin

The pregnancy hormone human Chorionic Gonadotropin (hCG) is produced by Langerhans cells in the syncytiotrophoblast of the placenta. It is very similar to LH in structure and binds to the LH receptor, but with a half-life of 36 h has a longer effect in duration. Despite the beta subunit of hCG is very similar to LH, it has an additional 24 amino acids. The sugar portions are also different. The different composition of the oligosaccharides is responsible for the prolonged plasma half life of hCG.

Administration of hCG is widely used in assisted reproduction to promote the final stages of follicular maturation and progression of the immature oocyte at prophase I through meiotic maturation to reach metaphase II. The completion of the meiotic process takes approximately

36 hours and, in the absence of follicular aspiration at oocyte retrieval, ovulation will ensue approximately 4 hours later.

Because of the long half-life plasma levels of hCG remain high for several days (see Table 3) and can improve luteal function, hCG is also believed to have a direct positive effect on endometrial receptivity [13]. Luteal phase support by hCG is equally effective or superior to Progesterone, but exposes to the risk of OHSS.

3.1. Physiology

hCG administration can replace the LH peak in the middle of the ovarian cycle and helps to improve luteal function. However, it cannot prevent regression of the corpus luteum.

3.2. Pharmacology

hCG serum concentrations 24 hours after i.m. injection [14]:

- 120 mIU/ml β-hCG after administration of 5000 IE hCG
- 240 mIU/ml β-hCG after administration of 40,000 IE hCG
- 500 mIU/ml β-hCG after administration of 80,000 IU hCG

- Half-life (Serum): initial half life 5.6 h; second half-life 23.9 h [15].

After pregnancies or miscarriages serum hCG can be detected for up to four weeks. The same problem occurs following administration of hCG to trigger ovulation in assisted reproduction in patients at risk for ovarian hyperstimulation.

3.3. Products available on the Market

The choriongonadotropin currently on the market is human derived from urine of pregnant women (Brevactid, Predalon) or manufactured using recombinant technology (Ovitrelle®) (Tab. 4).

Preparations of urinary hCG are marketed in vials of 1500 or 5000 IU. The SMPC of these products advise intramuscular injection. Since there are no proven differences in clinical performance subcutaneous administration is widely used.

Recombinant chorionic gonadotropin (Ovitrelle®) syringes or disposal pens contain 250 µg of product, which is equivalent to 6500 IU of hCG

3.3.1. Approved Indications

- Women undergoing superovulation prior to assisted reproductive techniques such as *in vitro* fertilisation (IVF)
- Anovulatory or oligo-ovulatory women
- Luteal phase defect in anovulatory or oligo-ovulatory patients after stimulation of follicular growth

Table 4. Choriongonadotropin. © Thomas Rabe

Brand-Name (Company)	Preparation	Dose	Approved indication
Otrivelle® Ovitrelle® 250 µg/0.5 ml solution for injection pre-filled syringe (MerckSerono) Ovitrelle® 250 µg solution for injection pre-filled pen (MerckSerono)	Each pre-filled pen contains 250 µg Choriongonadotropin alfa (equals 6500 IU)	250 µg oder 6500 IU 24–48 h after last FSH adm. see SMPC	– Adult women undergoing superovulation prior to assisted reproductive techniques such as <i>in vitro</i> fertilisation (IVF): Ovitrelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth. –Anovulatory or oligo-ovulatory adult women: Ovitrelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory women after stimulation of follicular growth.
Brevactid® 1500 IU (Ferring Pharmaceuticals) Brevactid® 5000 IU (Ferring Pharmaceuticals)	1 vial with dry substance: Choriongonadotropin 1500 IU 1 vial with dry substance: Choriongonadotropin 5000 IU	see SMPC see SMPC	In the female: Sterility due to the absence of follicle-ripening or ovulation. In combination with FSH or HMG, promotion of controlled superovulation
Predalon® 5000 IU Pregnyl® powder and solvent (MSD)	1 vial of dry substance: Choriongonadotropin 5000 IU	see SMPC	In the male: Hypogonadotropic hypogonadism. Delayed puberty associated with insufficient gonadotrophic pituitary function. Sterility in selected cases of deficient spermatogenesis.

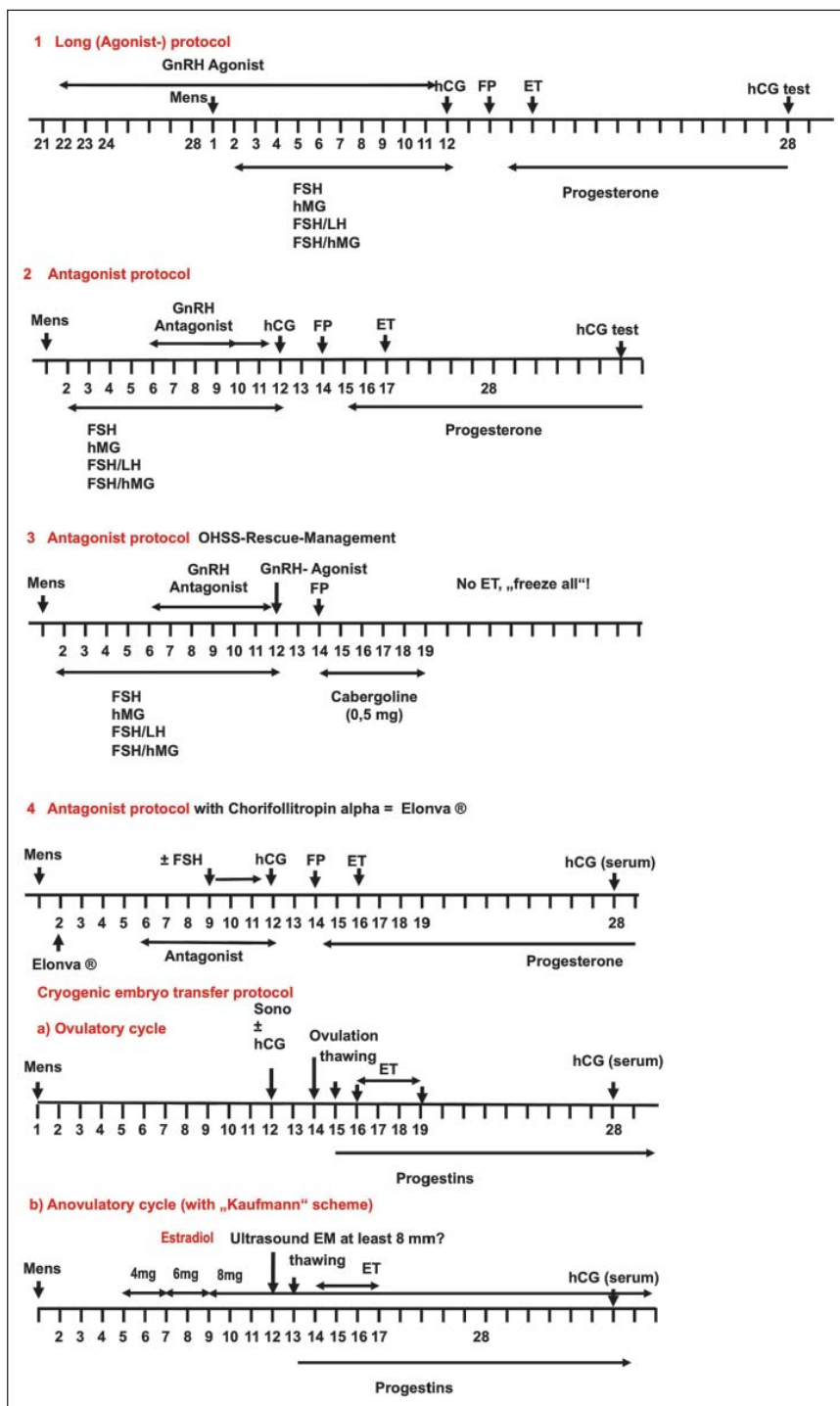


Figure 7. Stimulation regimens for controlled ovarian hyperstimulation in assisted reproduction. HMG: Human Menopausal Gonadotropin; FSH: follicle stimulating hormone; LH: luteinizing hormone; GnRH: Gonadotropin Releasing Hormone; Mens: Menstruation; hCG: Human Chorionic Gonadotropin; FP: follicle puncture; ET: embryo transfer (das 2–5 after FP). © Thomas Rabe.

3.4. Dosage

3.4.1. Triggering

For triggering ovulation, the dose recommendation is one vial of 250 µg Ovitrelle (equivalent to 6500 IU hCG) to be administered 24–48 hours after optimal stimulation of follicular growth is achieved. The recommended dose for

urinary preparations registered is one subcutaneous or intramuscular injection of maximally 10,000 IU (2 doses of Brevactid).

Intramuscular injection of 10,000 IU hCG leads to an initial rise of bloodplasma levels that are 20 times higher than

the maximum LH-Peak during spontaneous ovulation.

3.4.2. Luteal Phase Support

Treatment of luteal phase defects with hCG is possible with administration of 1500–5000 IU every 2–3 days for three times. However, low dose hCG every third day 1000 IU, 500 IU and 250 IU combined with progesterone might be sufficient to sustain corpus luteum function in GnRHa triggered cycles [16].

Support by hCG is equally effective or superior to progesterone but exposes to the risk of OHSS. For patients at risk for OHSS luteal support with progesterone alone is safer [17].

3.5. Clinical Advice

The timing of induction of ovulation with hCG depends on the stimulation protocol. Without stimulation follicle size should be at least 18–22 mm. After stimulation with Clomifen follicle size should be 18–24 mm, after stimulation with FSH or hMG it should be 16–18 mm.

3.6. Contraindications

- Patients at risk for Ovarian Hyperstimulation syndrome (OHSS)
- Hypersensitivity to the active substance or to any of its excipients
- Unwanted side effects: Ovarian Hyperstimulation syndrome (OHSS)

4. Ovarian Stimulation Protocols

In order to achieve a successful outcome of ART (IVF/ICSI) or non ART treatments (ovulation stimulation medications for timed intercourse or intrauterine inseminations) it is important to choose a suitable stimulation regimen. See Figure 7 for different stimulations regimens in ART.

Age, basal FSH level and bodyweight are variables known to affect ovarian response. AFC (antral follicle count) and AMH (Anti muellerian hormone) also should be taken into account in order to choose the correct dose for the individual patient.

The lowest effective dose in relation to the treatment objective should be used. FSH and hMG preparations can be dosed equally and are applicable for single use

or may be combined with each other. This also applies to recombinant fixed-dose combinations and long-acting FSH preparations.

There are no confirmed differences in safety, purity, or clinical efficacy among the various available urinary or recombinant gonadotropin products [18].

In a step-up regimen patients start with a lower dosage in order to avoid hyperresponse of the ovaries. The dosage as well as the intervals can be adjusted individually during stimulation. In order to achieve a maximum amount of recruited follicles in a step-down protocol patients start with a higher dosage and then decrease the dosage step by step in order to avoid hyperstimulation.

The initial hormonal situation of the patient influences the outcome of hormonal stimulation to a great extent.

Women with normogonadotropic infertility such as polycystic ovary syndrome (PCOS) are more likely to unfavorable reactions on stimulation with gonadotropins. Individual doses need to be adjusted carefully.

Patients with hypogonadotropic hypogonadism frequently need higher doses. However, ovulation- and pregnancy rates are better than in women with other causes of infertility.

4.1. Pulsatile GnRH Therapy

Patients with anovulation due to primary or secondary hypothalamic amenorrhoea may benefit from pulsatile GnRH stimulation with comparable efficacy to hMG [19]. GnRH pulsed doses are administered via subcutaneously implanted mini-osmotic pumps every 90 minutes. The system needs to be replaced every three days. Doses and duration of therapy can be adjusted individually.

4.2. Stimulation with hMG/hCG

Evaluating clinical studies on ovarian response the initial hMG dose should be 150 IU hMG without GnRH cotreatment and 225 IU/day in IVF protocols with GnRH [20]. For non ART treatment in hypogonadotropic patients up to 150 IU hMG is given from day three of the menstrual cycle. In patients with amenorrhoea stimulation can start at any time when the endometrium is flat.

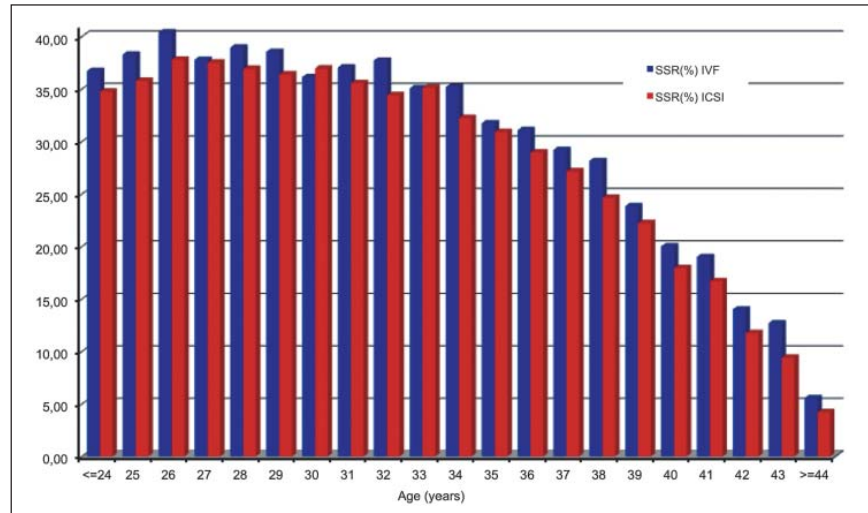


Figure 8. Pregnancy rates (in %) related to age and therapy (IVF or ICSI). Reprint from [Bühler K, et al. DIR Annual 2011. J Reproduktionsmed Endokrinol 2012; 453–84].

Normogonadotropic patients start with 75–150 IU hHG/day for non ART treatment. If more than 75 IU hMG have to be applied it is recommended to split into morning and evening doses. However, age > 35 years, elevated basal FSH levels and bodyweight are reasons to consider an increase in the initial hMG dose for IVF protocols. There is no proof of clinical benefit for doses higher than 300 IU. Some authors might still go up to 450 IU.

4.3. Stimulation with FSH

From day 3 to 9 of the menstrual cycle dependent on age, AFC, AMH and bodyweight up to 100 IU of FSH might be injected daily for timed intercourse or intrauterine inseminations and up to 300 IU for IVF/ ICSI. In most cases a step up protocol is used for adjustment of dosing. It is not yet clear whether patients with elevated LH/FSH quotients (> 2) and PCOS might benefit from stimulation with FSH alone.

4.4. Combined FSH/hMG/rec-LH Stimulation

In controlled ovarian stimulation trials fertilization rates were significantly lower in hypogonadotropic patients with a periovulatory LH ≤ 3 mIU/ml stimulated with FSH alone. Thus, if the LH level is < 3 mIU/ml when stimulation starts hMG or rLH is indicated. If the level is between 3–5 mIU/ml additional LH is not essential. [21]. Subgroups of women who may benefit from urinary gonadotropins (hMG and not uFSH) for ovarian stimulation in ART cycles are:

- hypogonadotropic patients,

- normogonadotropic women with over down-regulated cycles,
- young women with poor ovarian reserve or with ovarian resistance and
- women in an advanced reproductive age [22]. However, there is a small therapeutic window. If LH exceeds the threshold level it might be detrimental to follicular development. A FSH:LH ratio of 3:1 has been shown to improve results [23].

4.5. Gonadotropins and GnRH-Protocols

Controlled ovarian stimulation for ART treatment inevitably requires the use of either GnRH agonists or antagonists in order to prevent premature luteinization of follicles.

In the **long GnRH agonist protocol** (long protocol, GnRHa long) GnRHa treatment is initiated in the mid-luteal phase of the preceding cycle at least 10–14 days before stimulation with gonadotropins starts. The protocol allows both physicians and patients to schedule the start of stimulation according to their needs. However, for potential high-responder patients there are limited possibilities to avoid ovarian hyperstimulation syndrome. According to the annual report of the German IVF Register (D.I.R.) the long-protocol was the second most used regimen in Germany in 2013. It has been used in 27.2% (2402 of 8824) IVF cycles and 28.6 % (8784 of 30,710) ICSI cycles.

In the **short protocol** the agonist is initiated in the early follicular phase (day 1 to 3 of the cycle).

Table 5. Clinical pregnancy rate (CPR) as a function of the stimulation protocol 2013 (prospective data). From [Blumenauer V, et al. DIR Annual 2013 – German IVF-Registry. J Reproduktionsmed Endokrinol 2014; 11: 257.

	IVF							Total
	u-FSH	rec-FSH	hMG	recLH & recFSH	recFSH & hMG	Other*	No Info.	
Short GnRHa	3	226	302	32	103	1	2	669
Transfer Rate (%)	100	93.78	91.24	91.43	91.96	100	100	91.77
CP/ET (%)	66.67	28.76	32.12	43.75	20.39	0	0	29.75
Long GnRHa	88	1218	537	175	361	19	4	2402
Transfer Rate (%)	89.80	88.58	92.91	89.29	93.04	61.29	100	89.96
CP/ET (%)	37.50	39.49	33.15	34.29	34.63	36.84	25	36.84
No GnRHa-Analoga	20	245	203	64	132	14	161	839
Transfer Rate (%)	86.96	92.11	90.63	98.46	84.08	93.33	72.20	86.23
CP/ET (%)	45.00	35.10	34.48	29.69	34.09	28.57	19.88	31.59
GnRHa-Antagonists	83	2,79	923	517	495	88	18	4914
Transfer Rate (%)	93.26	86.86	86.97	84.20	86.54	83.81	60	86.46
CP/ET (%)	38.55	34.91	28.88	26.89	31.92	31.82	22.22	32.59
Total	194	4479	1965	788	1091	122	185	8824
	ICSI							Total
	u-FSH	rec-FSH	hMG	recLH & recFSH	recFSH & hMG	Other*	No Info.	
Short GnRHa	27	727	733	87	336	63	21	1994
Transfer Rate (%)	84.38	90.65	91.51	90.63	98.82	53.39	94.65	90.51
CP/ET (%)	18.52	24.48	23.87	24.14	14.88	17.46	42.86	22.52
Long GnRHa	139	4446	1702	691	1646	139	21	8784
Transfer Rate (%)	94.56	93.72	93.16	90.45	91.70	89.68	80.77	92.87
CP/ET (%)	39.57	35.70	31.37	31.69	33.05	30.94	38.10	34.04
No GnRHa-Analoga	38	870	572	147	563	38	624	2852
Transfer Rate (%)	88.37	89.60	86.14	84.48	83.28	97.44	84.26	83.81
CP/ET (%)	39.47	33.22	31.29	30.61	27.00	42.11	18.27	28.37
GnRHa-Antagonists	148	9323	2951	1957	2,278	325	98	1708
Transfer Rate (%)	90.24	89.92	89.78	85.76	83.69	89.04	79.03	88.44
CP/ET (%)	26.35	32.97	24.03	29.94	27.88	0	16.33	29.62
Total	352	15,366	5958	2882	4823	565	764	30,71

* e.g. u-FSH and hMG, Clomifen/rec-FSH, Clomifen/hMG etc.

In the **ultra-short protocol** a shorter period of GnRH-a administration for three days is chosen. The short GnRH protocols have been used in 6.5% of all ICSI cycles and 7.6% of all IVF cycles in Germany in 2013.

The **ultra-long-protocol** uses ovarian suppression for up to 6 months as a recognized treatment of endometriosis prior to the administration of gonadotropins. Stimulation starts 14 days after the last monthly injection of GnRHa and is similar to the long protocol.

GnRH-antagonist protocols are frequently used in women who are low-responders to ovarian stimulation or potential high-responders. The GnRH antagonist is usually initiated on the 6th day of FSH administration or when the dominant follicle has a diameter of at least 12 mm.

In the antagonist protocol triggering ovulation using GnRH agonists instead of hCG can prevent severe ovarian hyperstimulation syndrome (OHSS).

Because of impaired luteal function and in high-risk patients it seems prudent to freeze all embryos for future transfer. In 2013 the GnRH-antagonist protocol was the most commonly used protocol according to the D.I.R annual report. It has been used in 55.7% (4914 of 8824) IVF cycles and 55.6% (17,080 of 30,710) ICSI cycles.

New IVF protocols using less gonadotropins and an GnRH antagonist starting at the stage of a dominant follicle (modified natural cycle) or no gonadotropins at all (natural cycle IVF) have also been established and are promising with regard to saving costs and avoiding side effects in certain patients. To date compared to

conventional protocols, there is no reported benefit as far as life-birth-rates are concerned.

4.6. Results of Ovarian Stimulation for Assisted Reproduction

Controlled ovarian hyperstimulation protocols for assisted reproduction aim at retrieval of as many mature oocytes as it is safe for the patient. Pregnancy rates correlate directly with the number of mature oocytes (MII). The German IVF Register shows in 232,869 cycles that 10–15 MII oocytes lead to optimal pregnancy rates [24]. Data from the UK registry underline the positive correlation between the number of oocytes and life birth rates [25]. Nonetheless, of course the age of the patient determines the final success of fertility treatment. According to the German IVF registry assisted reproductive techniques can achieve the age

related spontaneous pregnancyrate (see Fig. 8).

The German IVF-Registry (D.I.R) collects electronic data for each initiated treatment cycle since 1996. Meanwhile, more than 1.2 million ART cycles have been documented in the database. The prospective documentation as well as the cycle by cycle data collection are of particular value and make the D.I.R an internationally recognized resource.

Looking at the results for different protocols one might think different medications could influence pregnancyrates (Tab. 5). However, a big bias has to be taken into account. Allegedly less expensive urinary preparations are far more likely to be prescribed to patients with advanced reproductive age. This might account for the significantly lower pregnancy rates.

In poor responders a switch to antagonist protocols is very common [26]. A novel area of interest for the stimulation with gonadotropins during the last years has been oocyte retrieval for cryopreservation by vitrification within the Fertiprotect project or for the so called "social freezing".

4.7. Ovarian Hyperstimulation

Ovarian Hyperstimulation Syndrome (OHSS) is a potentially life threatening complication which plagues stimulation with gonadotropins. The incidence is 0.5–2%. The exact aetiology of OHSS is still unknown. Although rare cases of OHSS after spontaneous conception have been reported, it is a mainly iatrogenic condition of capillary hyperpermeability with a fluid shift from the intravascular compartment into the third space. OHSS can often be foreseen and prevented. It does not occur if hCG is withheld. Figure 9 shows first steps in the pathophysiology of OHSS. High levels of estradiol can affect capillary permeability yet symptoms of OHSS will not occur unless hCG is present. The endothelium as well as the ovary is a primary target for hCG. Under the influence of hCG secretion of VEGF, upregulation of VEGF 2 receptor mRNA, activation of the renin-angiotensin system, the kinin-kallikrein system together with releasing of interleukins [6, 18], endothelial-cell adhesion molecules, von Willebrand factor, angiogenin and

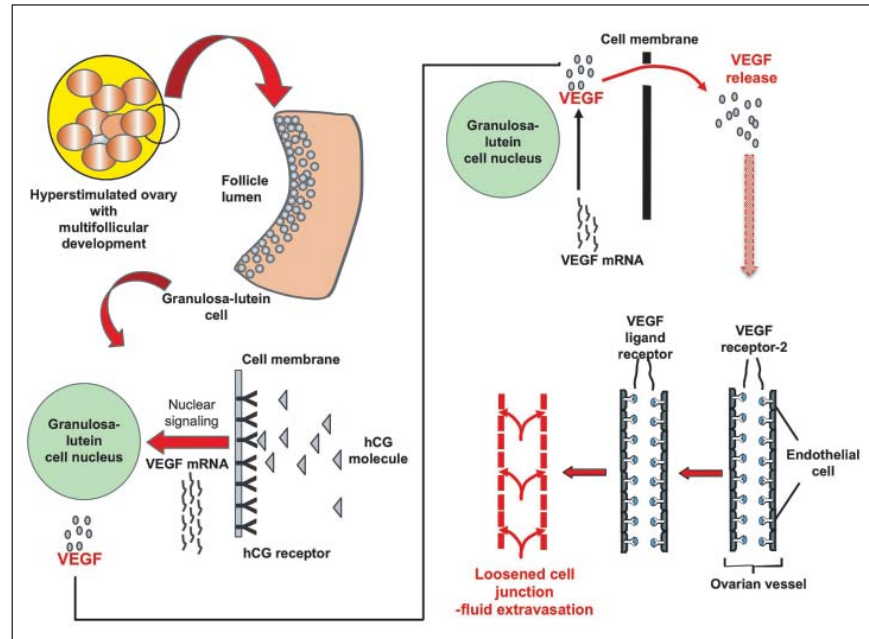


Figure 9. Pathophysiology of ovarian hyperstimulation (OHSS). Mod. from [Soares SR, et al. Targeting the vascular endothelial growth factor system to prevent ovarian hyperstimulation syndrome. Hum Reprod Update 2008; 14: 321–33] with permission of Oxford University Press.

Table 6. Risk factors for ovarian hyperstimulation syndrome (OHSS). © Thomas Rabe

Risk factors	Limits
Primary Risk factors (dependent on patients)	
High AMH-level	> 3.36 ng/ml
Age	> 33 years
History of OHSS	moderate or severe cases, especially when hospitalization was required
PCO(S)	> 24 antrafollicles in both ovaries
Secondary Risk factors (dependent on ovarian response) On the day of hCG administration	
Number of follicles	≥ 13 follicles ≥ 11 mm in diameter > 11 follicles ≥ 10 mm in diameter
Rapid rise of rE_2 -levels and great number of mature follicles	Estradiol 5000 pg/ml and/or ≥ 18 follicles = danger of severe OHSS
Number of oocytes retrieved	> 11 Oocytes
High VEGF-levels	
High Inhibin-B levels	High levels on day 5 of stimulation and on day of oocyte retrieval
hCG for Luteal phase support	
Pregnancy with high endogenous hCG-levels	

AFC: Antrafollicle Count; AMH: Anti-Muellerian Hormone; E_2 : Estradiol; hCG: human Chorionic Gonadotropin; OHSS: ovarian hyperstimulation syndrome; PCO: polycystic ovaries; PCOS: polycystic ovary syndrome; VEGF: vascular endothelial growth factor

endothelin-1 takes place in the ovary. Of all the different vasoactive components, vascular endothelial growth factor (VEGF) is probably the most important mediator and the most responsible for increased capillary permeability. It acts through the VEGF receptor-2 or high affinity receptors (KDR and flt 1) [27].

The shift of fluid and proteins into the third space may result in accumulating ascitic fluid in the abdominal, pleural or pericardial cavity and causes increasing hemoconcentration. Arterial hypotension caused by intravascular hypovolaemia can induce arterial vasoconstriction and affect renal function. As a result, sodium and water are retained. Oliguria

Table 7. Clinical Symptoms and Laboratory Parameters in Ovarian Hyperstimulation Syndrome. © Thomas Rabe. ARDS: acute respiratory distress syndrome.

Classification	I mild	II moderate	III severe
Ovarian enlargement	5–12 cm	> 12 cm	Variable
Abdominal distention	Moderate	Severe	Tense
Clinical ascites	None	Yes	Tense
Hydrothorax	None	Possible	Yes
Pericardial effusion	None	Infrequent	Infrequent
Decrease renal function	None	Infrequent	Frequent
Renal Failure	None	None	Possible
Thromboembolism	None	None	Possible
ARDS	None	None	Possible
Hemoconcentration	Hct < 45%	Hct > 45%	Hct < 55%
WBC/ml	< 15,000	> 15,000	> 25,000
Liver enzymes	Normal	Elevated	Elevated
Creatinine (ng/ml)	< 1.0	1.0–1.5	> 1.6
Creatinine clearance	> 100	50–1000	< 50

Table 8. Classification of OHSS symptoms. © Thomas Rabe

OHSS Classification	OHSS Symptoms	Laboratory parameters
Mild – OHSS I	Abdominal distension/discomfort Mild nausea/vomiting Diarrhea Enlarged ovaries in US	No changes
Moderate – OHSS II	OHSS I + in addition: Ascitic fluid in US	Hemoconcentration: elevated hematocrit (hct > 41%) Leucocytosis (> 15.000) Hypoproteinaemia
Severe – OHSS III	OHSS I + II + in addition: Clinical ascites Hydrothorax/Pleural effusion Dyspnea Oliguria/anuria Nausea and vomiting Severe abdominal distension/pain Hypotension Rapid increase of weight (> 1 kg in 24 hours) Syncope Venous thromboembolism	Hemoconcentration (hct > 55%) Leukocytes > 25.000 Creatinine clearance < 50 ml/min Creatinine > 1,6 Na ⁺ < 135 mMol/l K ⁺ > 5 mMol/l Rise of liver enzymes
Critical	Anuria, acute renal failure Cardiac arrhythmia Thromboembolism Pericardial effusion Massive hydrothorax Stroke ARDS (Adult respiratory distress syndrome) Sepsis	Deterioration of serum parameters

and renal failure are key features of life-threatening OHSS. Increasing hemoconcentration also leads to hypercoagulability of the blood with the severe risk of thromboembolic phenomena.

Most of the time, OHSS is self limiting, in rare cases symptoms persist until delivery.

To date there are no consistent standards of classification and treatment. Consensus over an interdisciplinary approach yet has to be achieved.

4.7.1. Risk Factors and Prevention

Primary prevention aims at identifying patients at risk for developing OHSS. For potential high-responders the antagonist

protocol with tailored dosing of gonadotropins in a chronic low-dose step-up regimen should be preferred. Strict monitoring of cycles in these patients is vital.

There is a great individual variation in the ovarian threshold for FSH in those women who will develop OHSS and those who will not. However, patients primarily at risk are:

- Young (< 35 years)
- Low body weight
- PCOS or PCO-like ovaries and/or hyperandrogenism
- High AMH-level (> 5 ng/ml)
- Previous history of OHSS

Secondary risk factors during stimulation and after oocyte retrieval are:

- High serum E2 (> 2000 pg/ml)
- Multiple follicle development
- Pregnancy
- hCG luteal supplementation (see also Table 6)

Secondary prevention:

a) Coasting: When estradiol concentrations rise to more than 3000 pg/ml gonadotropin stimulation can be withheld and hCG administration delayed until E2 levels decrease. However, there is no sufficient evidence on the safety and efficacy of this method [28].

b) Agonist trigger: Triggering of ovulation with a GnRH agonist is only possible in the antagonist protocol and can prevent OHSS totally. However, the luteal phase is rendered insufficient. To date, cryopreservation of pronuclei (PN) seems to be the best and safest approach for high-risk patients [29]. If an embryo transferral is desired within the same cycle additional luteal phase support is inevitable. There is no consensus on what form this should take.

c) Reduced dose of hCG and avoidance of giving hCG as luteal support: If agonist triggering is not an option i.e. in a GnRH protocol several investigators have assessed lower doses of 5000 IE hCG to be safe and efficient. Before very low doses of hCG can be recommended further study needs to be done on the increased risk of cycle cancellations. Progesterone administered vaginally can replace hCG.

d) Dopamine agonists: The dopamine agonist Cb2 appears to be effective in

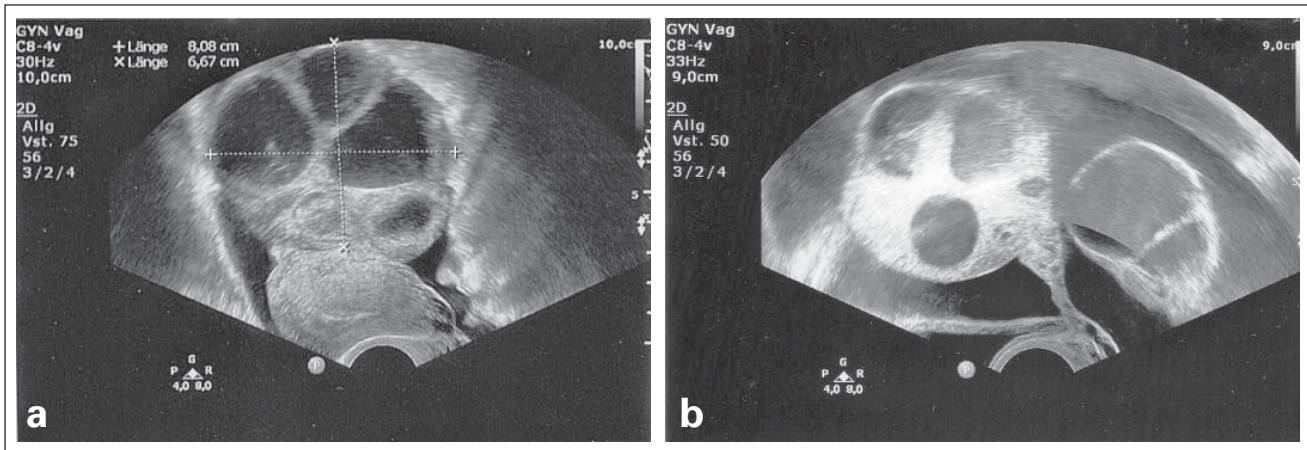


Figure 10. Ovarian hyperstimulation. (a): Polycystic ovary and uterus. (b): Enlarged right ovary with an increased risk of torsion, enlarged left ovary with ascites. Reprint with permission of N. Sängér.

controlling LH release in PCOS patients and acts at the VEGF receptor. In some studies oral administration of 0.5 mg Cabergoline for 8 days from the day of oocyte retrieval appears to be effective in reducing but not eliminating the incidence of moderate OHSS [30, 31] (<http://www.ivf-worldwide.com/education/ivf-complications/ovarian-hyperstimulation-syndrome-ohss.html>).

OHSS might be classified as **early-onset** due solely to the injection of hCG or **late-onset** caused by the added effect of the hCG by the trophoblast of the developing pregnancy. According to the severity of symptoms OHSS is also classified as (I) **mild**, (II) **moderate** or (III) **severe**. The severe form may be further sub-classified based on the severity into a critical state (Tab. 7, 8).

As long as the pathophysiology of OHSS remains unclear, treatment can only be empiric. To date there are no consistent standards of treatment. Consensus over an interdisciplinary approach yet has to be achieved. Especially for patients with severe OHSS requiring intensive care experts in renal, anaesthetic and cardiac medicine familiar with the peculiarities of OHSS need to be involved [32].

4.7.2. Management of OHSS I–II

Even in the mildest cases of OHSS

- high fluid- and protein-intake,
- weight control,
- investigation of hematocrit and hemoglobin,
- abdominal girth,
- urea, creatinine, serum electrolytes,

– and basal liver function is recommended.

An US scan should assess ovarian size (Fig. 10) and degree of ascites or pleural effusion at least once a week or more frequently when symptoms occur. As long as the patient is asymptomatic clinical follow up can be ambulatory and should take place at least every two to three days. A pregnancy test (hCG) should be performed approximately ten days after the embryo transfer. If the patient is not pregnant symptoms will be self-limited but should be followed up until resolution. If the cycle is conceptual symptoms might deteriorate under the presence of endogenous hCG and close monitoring is inevitable.

If signs of hemoconcentration (hematocrit > 40–45%) or deterioration of any clinical symptoms occur or if there is any doubt about the compliance of the patient hospitalization is recommended.

Low-dose SC heparin or Low Molecular Weight Heparin (LMWH) like Clexane is recommended when signs of hemoconcentration are present (Fig. 11).

4.7.3. Management of OHSS III

Severe OHSS requires immediate hospitalization and treatment. Parameters of hemoconcentration and renal function (retention parameters, monitoring of fluid intake and output) have to be monitored closely. An acute shift of fluids from the intravascular compartment to the peritoneal and pleural cavity or pericardial effusion must not be underdiagnosed. The ultimate aim of all supportive

treatment is prevention of deterioration into life threatening stages with hematocrit > 55%, electrolyte imbalance, serum creatinine levels > 1.6 mg/dl, respiratory distress, oliguria and avoidance of thromboembolism (Fig. 11).

4.7.4. Management of Oliguria and Hemoconcentration

Intravenous fluid therapy with crystalloids ideally 1.5 l to > 3 l NaCl is an important baseline therapy but rarely sufficient. Plasmaexpanders can be used when adequate fluid balance cannot be restored by crystalloids alone. Hydroxyethyl starch (HES) 33 ml/kg, fresh-frozen plasma, human albumin and mannitol (Osmofundin 125–250 ml as a short infusion) have all been utilized as plasma expanders through restoration of oncotic pressure.

However, the FDA and Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency has concluded that HES solutions should not be used in critically ill adult patients, including patients admitted to the ICU, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted.

Albumin (25–75 µg/day) is expensive and there is contradictory evidence whether its use is beneficial or not.

The discussion on the use of diuretics in patients with **oliguria** is controversial as this will further decrease intravascular fluid volume. However, when the patient has been fully hydrated and oliguria persists, furosemid 10 mg intravenously ev-

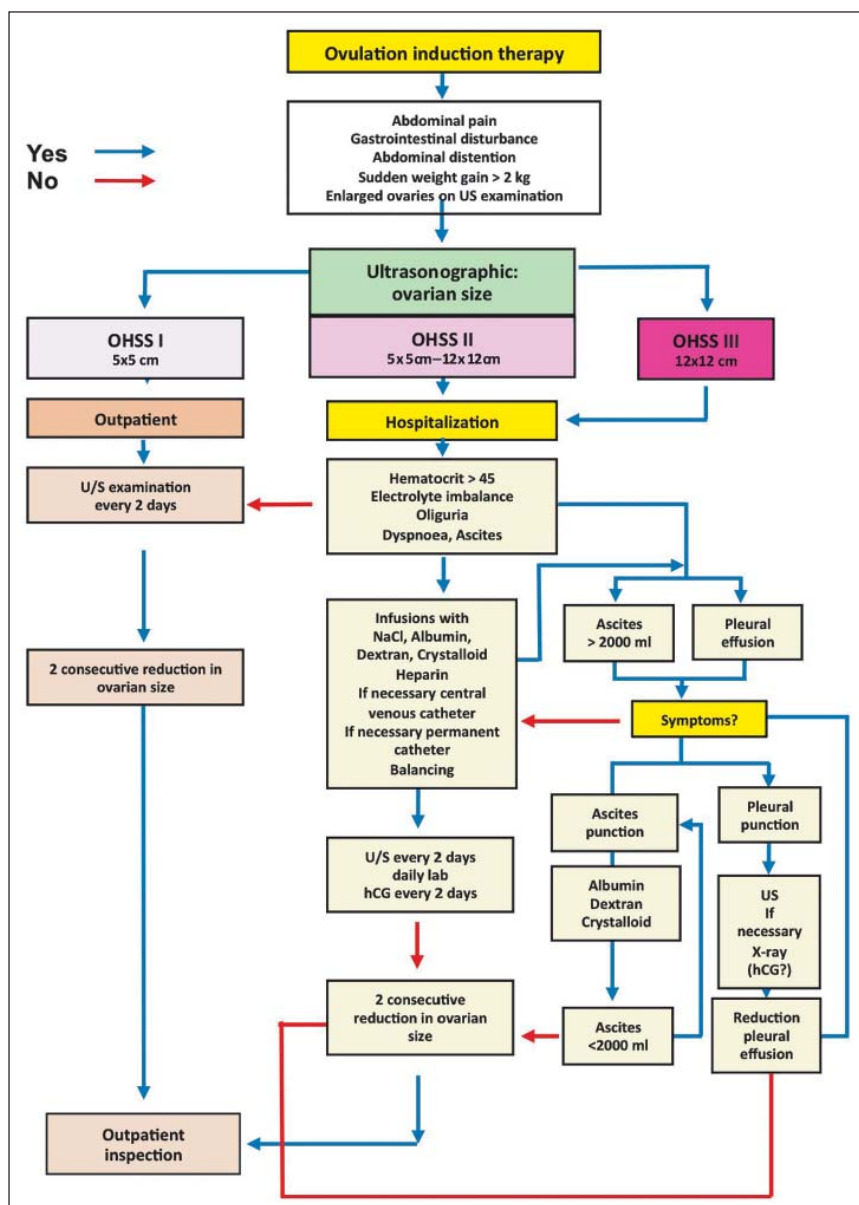


Figure 11. Management of ovarian hyperstimulation. © Thomas Rabe.

ery 4–6 hours might be applied with caution only until urinary output improves.

Since it is acting on the VEGF receptor low dose dopamine agonists might be more beneficial as far as intravascular fluid volume in patients with oliguria is concerned (2–4 µg/kg KG/min) might be applied continuously when urine output is < 60 ml/h.

Ascites can be managed expectantly as long as it is asymptomatic. When causing severe abdominal discomfort, dyspnea and/or impaired renal function is present, a tense ascites in a hemodynamically stable patient should be relieved slowly by ultrasound guided paracentesis.

Rapid drainage may cause acute deterioration in intravascular fluid volume. The maximum is 2–3 l in one puncture or 1l every day when repeated drainage is necessary. Close monitoring of electrolytes and proteins is necessary.

Thoracocentesis should be performed restrictively only when symptoms of dyspnea persist.

4.7.5. Additional Therapies

Prostaglandin synthesis inhibitors such as Indomethacin 2 × 100 mg/day can be administered in severe OHSS. It is not recommended during early pregnancy.

Counselling might also be advised in severe cases and long-term ICU treatment

5. New Developments

During the past decades approved preparations of FSH have been manufactured by three companies either solely focusing on recombinant sources from non-human cells (Follitropin alpha, Gonal-f®, Merck Serono; Follitropin beta, Puregon®, MSD) or urinary gonadotropins (Ferring). While urinary versions of FSH carry a heterogeneous but human glycosylation, the generally better biological safety of recombinant products made them the product of choice for most patients, despite a non-human glycosylation profile and higher product costs associated with the treatment.

The latest fundamental innovation in reproductive medicine was the launch of a long acting FSH molecule, Corifollitropin alfa (Elonva®), which reduces the frequency of injections and stress for patients.

Increasing demand for reproductive treatment worldwide account for several registration efforts on the way which will result into launches in the foreseeable future.

Novel drug development in the infertility field concentrates on less invasive delivery methods, such as the use of long-acting compounds or different routes of administration that may include transdermal, inhaled or oral agents [33].

5.1. Biosimilars

Biologicals like FSH are complex molecules and hence may be sensitive to changes in manufacturing processes. Biosimilars are officially approved protein based copies.

5.1.1. Bemfola

Bemfola (development code: AFOLIA) is a recombinant-human follicle-stimulating hormone (r-FSH) and has been developed as a biosimilar to Gonal-f®. It was granted marketing authorization by the European commission on 28.03.2014 based on the results of the FIN3001 (NCT01121666) trial.

372 women in the age of 20 to 38 were randomized 2:1 to receive a single, daily subcutaneous 150 IU dose of AFOLIA or the reference product Gonal-f®. AFOLIA demonstrated clinical and statistical equivalence to the reference product. The primary end point of the study was

to retrieve similar numbers of oocytes during a standard treatment in a long GnRH agonist protocol. The equivalence margins required that the difference in the number of oocytes retrieved not exceed ± 2.9 oocytes [34].

A similar clinical pregnancy rate per embryo transfer in first and second cycles (Bemfola: 40.2% and 38.5%, respectively; Gonal-f®: 48.2% and 27.8%, respectively) was reported in this in a recent publication about this study [35].

The results of the FIN3002 (NCT01687712) trial are expected to be published in 2015. The study began recruiting patients in November 2012. 1,106 women aged 35–42 years were randomised to one SC injection of 225 IU Gonal-f® (follitropin alfa) or 225 IU AFOLIA per day (initial dose) for the first 6 days. The dose can be increased to a maximum of 450 IU per day. The primary endpoint of this study is the clinical pregnancy rate.

5.1.2. Ovaleap

Ovaleap is a Biosimilar to Gonal-f® which has been approved by the European medicine agency in July 2013.

In a clinical trial with 299 women Ovaleap compared with Gonal-f® treatment resulted in a statistically equivalent number of retrieved oocytes. The average number of oocytes after stimulation with Ovaleap was 12.2 ± 6.8 and Gonal-f® 12.0 ± 6.8 (mean difference 0.03; -0.76 to 0.82).

However, this study has never been published in a peer-review journal. The product has also not been launched so far. Ovaleap is planned to be available as a pen which can be filled with 300, 450 or 900 IU units.

5.2. New FSH Molecules

At least two novel recombinant FSH preparations expressed by a human cell line are in advanced stages of development. FE 999049 (Ferring, Copenhagen) and FSH-GEX (Glycotope, Berlin).

5.2.1. FE 999049

This novel FSH preparation expressed by an immortalized human retinal cell line (PER.C6) has different pharmacodynamic and pharmacokinetic properties than the recombinant FSH follitropin alfa (Gonal-f®) expressed by CHO cell

lines. The ovarian responses by number of follicles and serum concentrations of inhibin B and estradiol, were higher with FE 999049 than with follitropin alfa, AUC and C(max) for the two latter being >1.6-fold greater with FE 999049 than with follitropin alfa [36].

In 25 patients an open cross-over study showed equal absorption and bioavailability of FE 999049 and follitropin alfa. Due to longer plasma half life exposition (AUC) was 50–60% higher [37].

So far one dose finding phase II study on FE 999049 has been completed (NCT01426386). 265 patients in a GnRH antagonist protocol received 5.2 µg/day, 6.9 µg/day, 8.6 µg/day, 10.3 µg/day or 12 µg/day FE 999049 vs 150 IU/day follitropin alfa. Patients were randomized according to AMH levels prior to the start of stimulation (< 15 pmol/l vs > 15 pmol/l). A linear dose dependent action profile was detected in both AMH groups. There was a significant effect of body mass on the FSH plasma levels. Patients with higher weight had lower plasma levels. In a multivariate analysis AMH levels could account for 35% of the inter-individual variation of the number of oocytes retrieved. Thus AMH is the strongest predictor of ovarian response to stimulation with FE 999049. A multinational randomised, controlled multicentre phase III trial comparing the efficacy and safety of FE 999049 with follitropin alfa (Gonal-f®) in controlled ovarian stimulation in women undergoing an assisted reproductive technology programme has been initiated in October 2013 and is still ongoing until 2016. In this study an individually dose of FE 999049 adjusted to body weight and AMH is administered [38].

5.2.2. FSH-GEX™

FSH-GEX™ is marketed as the first fully human glycosylated FSH (follicle-stimulating hormone), recombinantly expressed in human myeloma cells and glycooptimized to mimic endogenous human FSH.

A Phase II, multicenter, multinational, randomized clinical trial investigated the efficacy and safety of varying doses and schedules of FSH-GEX™ in comparison with daily 150 IU Gonal-f® in 247 women undergoing artificial insemination by intra-cytoplasmic sperm injection (ICSI)

treatment in an agonist protocol. FSH-GEX™ was tested in five dose cohorts, 52.5 IU, 75 IU, 112.5 IU and 150 IU daily doses, and 150 IU given every second day, compared to the standard daily dose of 150 IU Gonal-f®. The results have not been published in a peer review journal. The press release statement of Glycotype states that the data show that FSH-GEX™, even at half the biologic dose (75 IU FSH-GEX™), is at least as active as Gonal-f® (150 IU) in all FSH mediated parameters and endpoints, which might lead to a new therapeutical option with fewer injections. These data are supposed to confirm the preclinical, Phase Ia and Ib data regarding biological activity and clinical efficacy. No inductions of anti drug antibody (ADA) responses were observed in FSH-GEX™ patients. A phase III trial is anticipated [39].

5.3. Oral FSH

In 2009 a first proof-of-concept study on the development of orally active, low molecular weight gonadotropin has been reported in female volunteers [40]. Research is ongoing.

■ Conflict of Interest

No conflict of interest: C. Albring, A. Bachmann, K. Bühler, C. Gnath, K. König, J.-S. Krüssel, T. Rabe, N. Sängler, T. Steck, A. Weghofer, W. Würfel.

G. Griesinger: MSD, MerckSerono, Glycotope, Ferring, IBSA, VitroLife, Finox, ReprodWissen GmbH, TEVA GmbH: Consultancy; MerckSerono, Ferring: Grants; MSD, MerckSerono, IBSA, VitroLife, ReprodWissen GmbH: Payment for lectures.

H. Kentenich: Dr. KADE, Ferring, Merck Serono, MSD: lectures on congresses.

E. Merkle: MSD: speaker's fee, Advisory board, compensation for travel expenses; Shionogi: Advisory board, compensation for travel expenses.

T. Strowitzki: Clinical studies for rec FSH for Finox (Bemfola) and TEVA (Ovaleap), lecturer for Bayer Health Care.

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