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 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 of 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. LH: Lutropin alpha: Luveris® (Merck Serono)
- Compounds with more than one active agent:
  - human urinary-derived preparations: hMG HP: FSH, LH, hCG: 75 IU LH; Menogen 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 muellerian 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 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) of 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 GnRHa-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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Gonadotropins FSH and LH in Adult Women

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 estrogen levels.

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 purified. 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 Seagar-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 gonadotrophic 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 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 granulosacells 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-acetylgalactosamine, 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 Prostaglandine 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. Exogenous 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 an 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 Gonal f, Follitropin Beta (Puregon) and long-acting Corifollitropin 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

<table>
<thead>
<tr>
<th>Source</th>
<th>Abbreviation</th>
<th>Clinical relevance</th>
<th>Problems</th>
<th>Side-effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood of pregnant mares</td>
<td>PMSG</td>
<td>none</td>
<td>Supply could not meet demand</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands</td>
</tr>
<tr>
<td>Human pituitary glands</td>
<td>hPG</td>
<td>none</td>
<td>Contains extraneous urinary proteins, molecule might be altered due to different estrogen levels in pregnant women</td>
<td>see above</td>
<td>Tumors of the thyroid, ovaries, breast, uterus, or mammary tumors</td>
</tr>
<tr>
<td>Menotropins</td>
<td>hMG</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women, LH activity might be altered due to difference in estrogen levels between pregnant and non-pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
<tr>
<td>Highly purified urinary FSH</td>
<td>uFSH</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
<tr>
<td>Menotropins</td>
<td>hMG</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women, LH activity might be altered due to difference in estrogen levels between pregnant and non-pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
<tr>
<td>Highly purified urinary FSH</td>
<td>r-hFSH</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
<tr>
<td>Recombinant, not necessarily identical to natural FSH</td>
<td>r-hLH</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
<tr>
<td>Recombinant, not necessarily identical to natural FSH</td>
<td>r-hCG</td>
<td>available</td>
<td>Molecule i.e. sugarchain might be altered due to different estrogen levels in pregnant women</td>
<td>see above</td>
<td>Tumors of the pituitary or hypothalamic glands, primary ovarian failure, or abnormal uterine bleeding</td>
</tr>
</tbody>
</table>

**Side-effects and Contraindications**

- **Side-effects:**
  - Antibodies: see above
  - 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
  - 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
Gonadotropins FSH and LH in Adult Women

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 ± 2% can be achieved as opposed to a variability of + 5 to −20% in gonadotropins filled by bioassay [10].

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

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

<table>
<thead>
<tr>
<th>Substance</th>
<th>Brand name</th>
<th>Preparation</th>
<th>Dose</th>
<th>Approved therapeutic indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH</td>
<td>Luveris® (Merck Serono)</td>
<td>Powder and solvent for solution for parenteral injection. Each vial with dry substance contains Luveris® 75 IU</td>
<td>In association with FSH</td>
<td>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 &lt; 1.2 IU</td>
</tr>
<tr>
<td></td>
<td>Lutropin alpha</td>
<td>Powder and solvent for solution for parenteral injection. Each vial with dry substance contains Lutropin alpha 75 IU</td>
<td>75–300 IU/day</td>
<td>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 for 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 in vitro fertilisation (IVF/ICSI). – Hypogonadotropic hypogonadism in men: hMG may be given in combination with human chorionic gonadotropin (e.g. Choriogon) for the stimulation of spermatogenesis. Patients with primary testicular failure are usually unresponsive. 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 in patients undergoing assisted reproductive technologies (ART) (e.g. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).</td>
</tr>
<tr>
<td>hMG</td>
<td>Menogon® HP Menopur® (Ferring pharmaceuticals)</td>
<td>Powder and solvent for solution for parenteral injection. Each vial with dry substance contains: Menopur® (hMG) 75 IU FSH and 75 IU LH, highly purified.</td>
<td>75–300 IU/day</td>
<td>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. 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. in vitro fertilisation/embryo transfer (IVF/ET), gamete intra-fallopian transfer (GIFT) and intracytoplasmic sperm injection (ICSI)).</td>
</tr>
<tr>
<td>FSH (urinary)</td>
<td>Brevelles® 75 IU</td>
<td>Each vial with dry substance contains: Brevelles® 82.5 IU equals 75 IU FSH</td>
<td>75–300 IU/day subcutaneously</td>
<td>In adult males: Deficient spermatogenesis due to hypogonadotropic hypogonadism.</td>
</tr>
<tr>
<td>Corifollitropin alpha</td>
<td>Eliantr® 100 µg/150 µg (MSD)</td>
<td>Solution for injection. Each prefilled syringe (0.5 ml) contains Corifollitropin alfa 100 µg/150 µg (MSD)</td>
<td>&lt; 60 kg 100 µg/&gt; 60 kg 150 µg single dose subcutaneously</td>
<td>In adult females: Puregon is indicated for the treatment of female infertility in the following clinical situations: – 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 in patients undergoing assisted reproductive technologies (ART) such as in vitro fertilisation (IVF), gamete intra-fallopian transfer and zona intra-fallopian transfer (ZIFT).</td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Puregon® 50 IU/0.5 ml</td>
<td>Solution for injection in cartridges: Puregon® 50 IU/0.5 ml</td>
<td>75–300 IU/day</td>
<td>In adult women: – Anovulation (including polycystic ovarian disease, PCOD) in women who have 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. 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 &lt; 1.2 IU/l. In adult men: – GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.</td>
</tr>
<tr>
<td>Follitropin beta</td>
<td>Puregon® 100 IU/0.5 ml</td>
<td>Solution for injection in cartridges: Puregon® 100 IU/0.5 ml</td>
<td>0.75–300 IU/day</td>
<td>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 in vitro fertilisation (IVF), gamete intra-fallopian transfer and zygote intra-fallopian transfer (ZIFT). Follitropin alfa 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 &lt; 1.2 IU/l. In adult men: – Follitropin alfa is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism.</td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Parasum® 75 IU/0.75 ml</td>
<td>Solution for injection in pre-filled pen of follitropin alfa* (equivalent to 75; 600; 1,250 IU)</td>
<td>75–300 IU/day</td>
<td>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 in vitro 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 &lt; 1.2 IU/l. In adult men: – GONAL-f is indicated for the stimulation of spermatogenesis in men who have congenital or acquired hypogonadotropic hypogonadism with concomitant human Chorionic Gonadotropin (hCG) therapy.</td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Parasum® 300 IU/1.5 ml</td>
<td>Solution for injection in pre-filled pen (MerckSerono)</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>Benfola® 75 IU/0.5 ml</td>
<td>Solution for injection in pre-filled pen (MerckSerono)</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Bemfola® 150 IU/0.75 ml</td>
<td>Solution for injection in pre-filled pen (MerckSerono)</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Biosimilar Benfola®</td>
<td>Solution for injection in pre-filled pen (MerckSerono)</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
<tr>
<td>FSH</td>
<td>Ovaleap® Biotech AG/Schweiz</td>
<td>Cartridges for use in pen</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
<tr>
<td>FSH (recombinant)</td>
<td>Biosimilar</td>
<td>Solution for injection in pre-filled pen (MerckSerono)</td>
<td>75–300 IU/day</td>
<td></td>
</tr>
</tbody>
</table>
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 aggravation 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
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 in structure and binds to the LH receptor, but with a half-life of 36 h, hCG 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

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.

3.3. 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>
<thead>
<tr>
<th>Brand-Name (Company)</th>
<th>Preparation</th>
<th>Dose</th>
<th>Approved indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otrivelle®</td>
<td>Each pre-filled pen contains 250 µg Choriogonadotropin alfa (equals 6500 IU)</td>
<td>250 µg or 6500 IU 24–48 h after last FSH adm. see SMPC</td>
<td>– Adult women undergoing superovulation prior to assisted reproductive techniques such as in vitro fertilisation (IVF): Otrivelle is administered to trigger final follicular maturation and luteinisation after stimulation of follicular growth. –Anovulatory or oligo-ovulatory adult women: Otrivelle is administered to trigger ovulation and luteinisation in anovulatory or oligo-ovulatory women after stimulation of follicular growth.</td>
</tr>
<tr>
<td>Brevactid® 1500 IU (Ferring Pharmaceuticals)</td>
<td>1 vial with dry substance: Choriogonadotropin 1500 IU</td>
<td>see SMPC</td>
<td>In the female: Sterility due to the absence of follicle ripening or ovulation. In combination with FSH or HMG, promotion of controls superovulation</td>
</tr>
<tr>
<td>Predalon® 5000 IU (Msd)</td>
<td>1 vial of dry substance: Choriogonadotropin 5000 IU</td>
<td>see SMPC</td>
<td>In the male: Hypogonadotrophic hypogonadism. Delayed puberty associated with insufficient gonadotropic pituitary function. Sterility in selected cases of deficient spermatogenesis.</td>
</tr>
</tbody>
</table>


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

Table 4. Choriongonadotropin. © 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 bloodplasmalevels 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 GnRHα 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 Clomifene 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 hypergonadotropic 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.

Normogonadotropic patients start with 75–150 IU hHMG/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 body weight 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 body weight 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 trails 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).

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].

J Reproduktionsmed Endokrinol_Online 2015; 12 (4) 369
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 pregnancy rate (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 pregnancy rates (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 Fertiproject 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 forseen 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 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...
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.

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

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

Table 8. Classification of OHSS symptoms. © Thomas Rabe

<table>
<thead>
<tr>
<th>OHSS Classification</th>
<th>OHSS Symptoms</th>
<th>Laboratory parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild – OHSS I</td>
<td>Abdominal distension/discomfort</td>
<td>No changes</td>
</tr>
<tr>
<td></td>
<td>Mild nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enlarged ovaries in US</td>
<td></td>
</tr>
<tr>
<td>Moderate – OHSS II</td>
<td>OHSS I + in addition: Ascitic fluid in US</td>
<td>Hemoconcentration: elevated hematocrit (&gt; 41%)</td>
</tr>
<tr>
<td></td>
<td>Leukoctysis (&gt; 15,000)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypoproteinemia</td>
<td></td>
</tr>
<tr>
<td>Severe – OHSS III</td>
<td>OHSS I + II + in addition: Clinical ascites</td>
<td>Hemoconcentration (hct &gt; 55%)</td>
</tr>
<tr>
<td></td>
<td>Hydrothorax/Pleural effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oliguria/anuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nausea and vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe abdominal distension/pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rapid increase of weight (&gt; 1 kg in 24 hours)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Syncopes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Venous thromboembolism</td>
<td></td>
</tr>
<tr>
<td>Critical</td>
<td>Anuria, acute renal failure</td>
<td>Deterioration of serum parameters</td>
</tr>
<tr>
<td></td>
<td>Cardial arrhythmia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thromboembolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericardial effusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Massive hydrothorax</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARDS (Adult respiratory distress syndrome)</td>
<td></td>
</tr>
</tbody>
</table>

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...
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 hemo-
globin,
- 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 (hemato-
crit > 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 Hemococoncentration

Intravenous fluid therapy with cristalloids 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 cristalloids alone. Hydroxyethyl starch (HES) 33 ml/kg, fresh-frozen plasma, human albumin and manni-
tol (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 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. Sänger.
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 continuosly 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 1 l 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 x 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
Biologics 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). An 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 culticentre 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 Glycotope 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 therapeutic 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-GEXTM 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

References:
Metwally M. Luteal phase support for assisted reproduction


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