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Pharmacology of medications used for ovarian stimulation

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The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, gonadotropins, and pulsatile gonadotropin releasing hormone (GnRH). Novel potential compounds and adjuvant treatment approaches are also discussed, such as kisspeptin agonists and androgens.

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Medications to stimulate the ovaries may be used to induce ovulation in patients with anovulatory infertility or to hyperstimulate the ovaries in a controlled fashion in ovulatory patients as part of assisted reproductive treatments (ART).
The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, gonadotropins, and pulsatile gonadotropin releasing hormone (GnRH). Novel potential compounds and adjuvant treatment approaches are also discussed, such as kisspeptin agonists and androgens.

Introduction

The central organ in female reproduction is the ovary, given that it is host to the female gametes, the oocytes, and because of its crucial role in the hormonal control of the menstrual cycle. As the end organ of the hypothalamic-pituitary-ovarian axis, hormonal events in the ovary control the cyclical changes

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in the endometrium. Through a complex interplay between the elements of the reproductive axis, the endometrium is prepared for implantation. The timing of the events during ovulation and the follicular–luteal transition ensures embryonic-endometrial synchrony and forms the basis for a successful pregnancy.

However, disorders of ovulation and the gradual depletion of ovarian follicles throughout the female reproductive lifespan can impair the normal physiologic processes and cause infertility. In some ovulatory disorders, treatment of the underlying cause can restore ovulation, such as in the treatment of hypothyroidism or hyperprolactinemia. When the entire hypothalamic-pituitary-ovarian axis is malfunctioning, such as in WHO I anovulatory infertility, treatment with pulsatile GnRH is indicated. Oral ovulation induction agents are commonly used for WHO II anovulatory infertility caused by polycystic ovary syndrome. Injectable gonadotropins to stimulate the ovaries are an integral part of assisted reproductive technology (ART) regimens for in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles.

The pharmacology of all current major medications used to stimulate ovarian function is reviewed in this article, including letrozole, clomiphene citrate, along with novel potential compounds and adjuvant treatment approaches.

Ovarian physiology

The ovary is the central organ in the hormonal control of the menstrual cycle, a highly regulated process with the goal of releasing a single mature oocyte. Over the course of a full cycle, major hormonal changes occur. The ovary is relatively hormonally inactive in the early follicular phase. With the progressive growth of a cohort of follicles under the influence of FSH, estradiol concentrations rise, in turn causing a suppression of serum FSH and LH concentrations. This leads to the selection of the dominant follicle, induction of LH receptors within it, and ovarian secretion of intrauterine growth factors such as insulin-like growth factor-1 (IGF-1). Estradiol concentrations continue to rise, ultimately causing a mid-cycle surge of LH through a switch in the feedback control of LH by ovarian hormones from negative to positive [1]. The LH surge induces a variety of changes in the ovary, including the final maturation of the oocyte and completion of the first meiotic division, and its release from the dominant follicle. Luteinization of granulosa cells in the dominant follicle gives rise to the corpus luteum, production site for progesterone, but also estradiol during the luteal phase [2].

If no fertilization occurs and the corpus luteum is not “rescued” by rising hCG concentrations from the syncytiotrophoblast, it regresses by apoptosis leading to decreased sex steroid levels. This causes the endometrium to slough. As the corpus luteum becomes progressively hormonally inactive (approximately 14 days after the LH surge), pituitary gonadotropins are freed from ovarian feedback and the next cycle is ready to begin.

Pathophysiology of disorders affecting the ovary

When the complex, tightly regulated processes in the ovary and its interplay with the other elements of the hypothalamic-pituitary-ovarian-endometrial axis malfunction, disorders of ovulation may occur. The World Health Organization (WHO) classified anovulatory disorders according to the type of defect in the hypothalamic–pituitary–ovarian axis ([3]; Table 1).

Disorders of ovulation may have hypothalamic origin (WHO class I anovulation). They may also be caused by the complex hormonal imbalances affecting the reproductive and metabolic systems in the polycystic ovary syndrome (PCOS; WHO class II anovulation) or by derangements in other hormone systems that can affect the reproductive axis, such as prolactin excess.

Depletion of the finite pool of follicles in the ovary results in hypergonadotropic hypoestrogenic anovulation (WHO class III anovulation). When this occurs prior to the age of 40, it is termed primary ovarian insufficiency (formerly known as premature ovarian failure).

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Table 1
Classification of ovulation disorders ([3]; with permission).

Hypogonadotrophic hypogonadism (World Health Organization group I)
• Idiopathic hypogonadotrophic hypogonadism
• Kallmann's syndrome (isolated gonadotrophin deficiency and anosmia)
• Functional hypothalamic dysfunction (e.g. excessive weight loss such as in anorexia nervosa, exercise, stress, drugs,
• iatrogenic)
• Pituitary tumour, pituitary infarct (e.g. Sheehan's syndrome)
Normogonadotrophic normogonadic ovarian dysfunction (World Health Organization group II)
• Polycystic ovary syndrome
Hypergonadotrophic hypogonadism (ovarian failure) (WHO group III)
• Genetic (e.g. Turner's syndrome)
• Autoimmune causes
• Infection (e.g. mumps oophoritis)
• Iatrogenic (e.g. surgical menopause, post-radiotherapy or chemotherapy)
• Idiopathic

(Not classified): Other endocrinopathies, such as hyperprolactinaemia, thyroid dysfunction, other conditions of androgen excess such as congenital adrenal hyperplasia and androgen-secreting adrenal and ovarian tumors.

Medications used to induce ovulation

Restoration of ovulation through causal treatment

When normal thyroid function is disturbed in either hyper- or hypothyroidism, ovulatory and therefore menstrual irregularities frequently occur, often before the onset of other symptoms [4]. Treatment of the underlying cause, such as thyroxine substitution in hypothyroidism, can restore a normal ovulatory pattern and reverse hormonal changes [5].

Hyperprolactinemia causes anovulation via inhibition of the release of gonadotropin-releasing hormone (GnRH) and may have a multitude of etiologies, such as a lactotroph adenoma [6] or the use of neuroleptic drugs [7].

The mainstay of treatment in patient with lactotroph adenomas, the most frequent cause of hyperprolactinemia, is dopamine agonist therapy [8]. Cabergoline, the currently recommended first line therapy, and bromocriptine, the recommended second choice agent, reduce tumor size of both micro- and macroadenomas [9], decrease prolactin concentrations and restore ovulatory function in this setting [10].

When treatment of the underlying cause is possible, this is the preferred option, given that removal of the inciting cause leads to restoration of monofollicular ovulation.

Restoration of ovulation in who I anovulation

In patients with WHO I anovulation, the entire reproductive axis is dormant, resulting in hypothalamic amenorrhea. In rare cases this may be secondary to congenital GnRH deficiency, which, if associated with anosmia, is termed Kallmann syndrome, a clinically and genetically heterogeneous disease [11].

More commonly hypogonadotropic hypogonadism is acquired and referred to as functional hypothalamic amenorrhea (FHA) [12]. This can occur as a result of severe energy restriction, increased energy expenditure, and stress, although a genetic predisposition has been identified [13]. The combination of low energy availability, menstrual dysfunction and low bone density is termed “female athlete triad” [14,15]. The decrease in hypothalamic GnRH secretion in FHA is caused by a disturbance in hormones controlling energy intake and output which are also reproductive regulators, such as leptin [16] and ghrelin [17].

In landmark experiments in the 1970s and 1980s on adult ovariectomized rhesus monkeys with hypothalamic lesions, it was discovered that intermittent pulsatile, but not continuous administration of GnRH led to the reestablishment of sustained elevated gonadotropin concentrations [18–20].

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Therefore the therapeutic substitution of GnRH for the purpose of ovulation induction in congenital GnRH deficiency and in FHA must also be cyclical. The prerequisite for this therapy is that the patient has normal pituitary function. Normal feedback mechanisms of the HPO axis are maintained, resulting in the induction of monofollicular ovulation in most cases. When exogenous gonadotropins are administered in this setting, normal feedback mechanisms are no longer intact, and the risk of multiple folliculogenesis, higher order multiple gestations, and ovarian enlargement, is increased [21].

Pulsatile GnRH can be given via intravenous or subcutaneous route. In the United States this is currently only possible in a research setting, whereas a commercially available subcutaneous pump is available for treatment of both men and women in Europe [22,23].

In one of the first reported clinical studies, 14 infertile women with FHA received pulses of 5–15 μg of GnRH administered subcutaneously by portable pumps at 90-min intervals in 36 cycles of treatment [24]. Ovulation occurred in 30 cycles (83%) and was followed by normal luteal function in 24. Singleton pregnancy occurred after 13 (54 per cent) of these cycles.

Pharmacologically, the active ingredient of the pulsatile GnRH pump, gonadorelin, is chemically and biologically identical with hypothalamic GnRH, a decapeptide with the sequence Pyr-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly. The subcutaneous GnRH pump available in Europe (Lutrelef®/Lutrepulse®, Ferring Pharmaceuticals, Saint-Prex, Switzerland) contains a total of 3.2 mg gonadorelin acetate. Pulses of 10, 15 or 20 μg are administered every 90–120 min over a period of 10–20 days via a remote-control pod. While the pump was usually continued during the luteal phase in the research setting, it is customary to discontinue the pulsatile GnRH administration after ovulation in the clinical setting, and support the luteal phase with human chorionic gonadotropin (hCG).

When access to pulsatile GnRH therapy is not available, ovulation induction with injectable gonadotropins is the second-best option, even though associated with a higher risk of ovarian hyperstimulation and multiple gestation [21]. Because luteinizing hormone tends to be especially low in the patient population with FHA [25], it is important to use a LH/FSH combination gonadotropin preparation such as human menopausal gonadotropin (hMG) for ovulation induction in this setting. Because of the chronically low estrogen concentrations, clomiphene citrate (CC) is usually ineffective in patients with FHA. In women with fluctuating or low but sufficient endogenous estrogen concentrations, CC may restore ovulation in some cases [26].

Ovulation induction in polycystic ovary syndrome (Pcos)

Clomiphene citrate

Clomiphene Citrate (CC) is a selective estrogen receptor modulator (SERM), with estrogen receptor agonist and antagonist properties [27].

Estrogen agonist actions occur at low endogenous estrogen concentrations, otherwise CC acts mainly as a competitive antagonist at the estrogen receptor [28]. CC is a racemic mixture of the two stereoisomers enclomiphene and zuclomiphene, with the former being the stereoisomer mainly responsible for its efficacy in ovulation induction [29]. CC is metabolized in the liver and excreted in the stool, with a relatively long half-life of 5–7 days [30]. The less potent stereoisomer zuclomiphene remains detectable for much longer periods of time, without major clinical relevance [31].

At the level of the hypothalamus, CC binds and depletes estrogen receptors. This leads to an inhibition of the negative feedback effect of circulating estradiol, which in turn increases the pulse frequency of hypothalamic GnRH. This results in increased LH and FSH production by the pituitary gland [32].

In women with polycystic ovary syndrome, CC is highly effective in inducing ovulation and was until recently recommended as the initial treatment of choice for most anovulatory or oligo-ovulatory infertile women [28,33], despite some data regarding potential detrimental effects on cervical mucus [34] and endometrial thickness [35] of debatable clinical impact.

A randomized multicenter trial comparing CC, the insulin sensitizer metformin, and both medications combined in 626 patients with the polycystic ovary syndrome found live-birth rates of 22.5%, 7.2% and 26.8% in the clomiphene group, metformin group, combination-therapy group, respectively. Among pregnancies, the rate of multiple pregnancy was 6.0% in the clomiphene group, 0% in the metformin group, and 3.1% in the combination-therapy group [36]. The authors reached the conclusion

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that clomiphene is superior to metformin in achieving live birth in infertile women with the polycystic ovary syndrome, although multiple birth is a complication.

Subsequent to this, however, another multicenter randomized controlled trial (RCT) by Legro et al. demonstrated that the aromatase inhibitor letrozole was superior to CC in patients with the polycystic ovary syndrome [37], resulting in a change in recommendation from CC to letrozole as the first line agent for ovulation induction in this setting.

Letrozole

Aromatase, a member of the cytochrome P450 superfamily, is the enzyme catalyzing the rate-limiting step in the biosynthesis of estrogens [38]. Also termed CYP19A1, aromatase is responsible for the aromatization of androgens into estrogens. Aromatase inhibitors are used in oncology as adjuvant therapy for postmenopausal women with breast cancer [39]. Given that aromatase inhibitors dramatically lower systemic estrogen concentrations, investigators attempted to use them for ovulation induction by preventing estrogen negative feedback on FSH [40,41]. Initial pilot studies demonstrated high rates of ovulation induction in patients with polycystic ovary syndrome using the aromatase inhibitor letrozole, with few side effects [40]. However, results from an abstract at the 2005 American Society of Reproductive Medicine (ASRM) meeting suggested an increased rate of cardiac malformations in babies born to women who underwent fertility treatment involving letrozole [41]. The abstract was never published, but it prompted the manufacturer of letrozole to issue a “black box warning” on its use in women with premenopausal endocrine status, as well as in lactation and pregnancy. Subsequent published research of higher quality than the 2005 abstract demonstrated that the incidence of congenital cardiac anomalies in babies born to mothers using letrozole is significantly lower than the one in babies born to mothers using CC [42], and lower than in the general population [43]. The finding of no increased risk of major congenital anomalies have since been supported by several other studies, including a large Japanese retrospective cohort study [44].

Although the clinical use of letrozole for ovulation induction in polycystic ovary syndrome slowed down following the manufacturer's warning, research into the use of aromatase inhibitors in this context continued.

In 2014, 750 women with polycystic ovary syndrome according to modified Rotterdam criteria were randomly assigned to receive letrozole or clomiphene for up to five treatment cycles in a double-blind, multicenter trial [37]. The cumulative live birth rate was 27.5% in the letrozole arm versus 19.1% in the clomiphene arm ($P = 0.007$); rate ratio for live birth, 1.44; 95% confidence interval, 1.10 to 1.87, Fig. 1 [37]).

There was no significant difference in the rates of overall congenital anomalies, pregnancy loss or twin pregnancy. Clomiphene was associated with a higher incidence of hot flushes, and letrozole was associated with higher incidences of fatigue and dizziness. The authors concluded that letrozole was

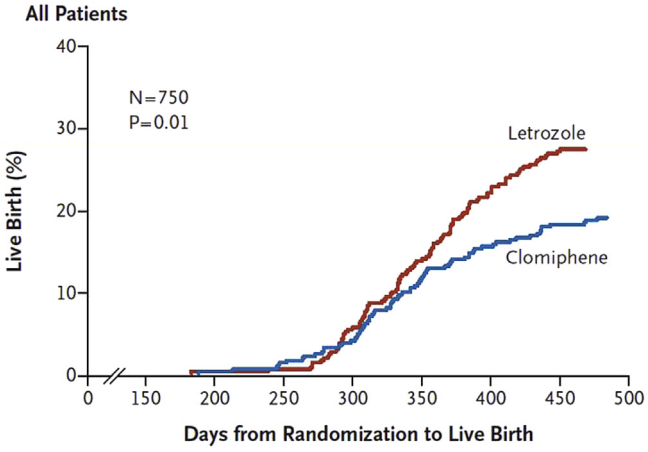

Fig. 1. Kaplan–Meier curves for live birth according to treatment group [37].

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associated with higher live-birth and ovulation rates among infertile women with the polycystic ovary syndrome. A Cochrane meta-analysis of a total of fourteen RCTs comparing letrozole versus clomiphene citrate (with or without adjuncts) followed by timed intercourse confirmed the finding of a higher pregnancy rate in the letrozole group [45,46]. This led to the current recommendation that letrozole be used as first-line agent in this clinical setting.

Gonadotropins

In the first half of the 20th century, it was discovered that gonadal function was regulated by the pituitary gland and that ablation of the pituitary resulted in gonadal atrophy [47]. Studies in dogs and other species demonstrated that transplantation of anterior pituitary tissue from sexually mature into sexually immature animals bestowed reproductive function on the recipient [48].

Initially termed prolan A and B by Zondek, two cyclically secreted gonadotropins were discovered in the urine and blood of women, and later renamed follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [48].

Ascheim and Zondek also discovered in the first half of the 20th century that the blood and urine of pregnant women contained a gonad-stimulating substance thought to be produced by the pituitary gland, but later shown to be produced in the placenta-human chorionic gonadotropin (hCG) [48]. Soon, the concept of the "two-step protocol" was introduced (1941)- ovarian stimulation using gonadotropins followed by triggering of ovulation using hCG. Gonadotropins for research and clinical use were initially extracted from swine and sheep pituitaries, then from the blood of pregnant mares (pregnant mare serum gonadotropin/PMSG). Although effective, PMSG carried the risk of provoking anti-species and anti-gonadotropin antibody formation, which could neutralize exogenous, but also endogenous gonadotropins. Therefore, purified human gonadotropins were isolated from human pituitary glands. The commercial application of human pituitary gonadotropins (hPG) was hampered by the limited supply, and came to an end when cases of Creutzfeld-Jakob disease occurred as a result of treatment with hPG [49]. The purification and isolation of gonadotropins from human menopausal urine was the next step in the pharmacologic evolution. The first source for human menopausal gonadotropin (hMG) production was an Italian nunnery, but quickly other production sites in various countries followed [47]. The purity of the initial batches of hMG was low, and early preparations contained a diverse mixture of substances including FSH, LH and hCG. Purification techniques improved and international standards for LH and FSH activity were developed. Polyclonal antibodies directed at LH or monoclonal antibodies specific to FSH were used to manufacture progressively more pure FSH preparations [50]. Finally, the emergence of DNA technology allowed for the advent of recombinant FSH preparations produced by transfecting expression vectors containing FSH-encoding genes into Chinese hamster ovary cells [51].

FSH, LH, hCG and thyroid-stimulating hormone (TSH) all share the same α subunit, but the glycoprotein hormones differ in the structure of the β-subunit which is non-covalently linked to it, and the carbohydrate moieties attached to the protein component of each hormone [52]. Whereas the identical α-subunit consists of 92 amino acids, the β-subunit of FSH, hCG, LH and TSH consist of 111, 121, 144 and 118 amino acids, respectively, and their structural differences, along with the degree of glycosylation, confer the differences in biological activity and receptor specificity [53]. Of these four glycoproteins sharing the same α-subunit, LH and hCG are the most structurally similar to each other: the β-subunit of LH is the same as hCG with 23 amino acids added and a different glycosylation profile, which accounts for the short half-life of LH (20 min) compared to hCG (24 h). Fig. 2 and Fig. 3 show the biochemical structure of human FSH and hCG (Figs. 2 and 3 [47], with permission).

Pharmacologically, gonadotropins bind to their specific extracellular receptors, which are transmembrane G protein-coupled receptors. Differences in receptor genotypes are associated with the response to glycoproteins, as in the case of FSH-mediated ovarian stimulation [54]. In healthy women undergoing ovarian stimulation, exogenous LH is not required in addition to FSH for follicular maturation [55]. Clinically, the gonadotropins LH and FSH can be used for ovulation induction in anovulatory patients, including those with polycystic ovary syndrome and those with hypothalamic anovulation. They are also an integral part of the controlled ovarian hyperstimulation (COH) in assisted reproductive technology (ART) such as in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) cycles. After ovarian stimulation with either FSH alone or FSH and LH, hCG is used to induce the final stage of

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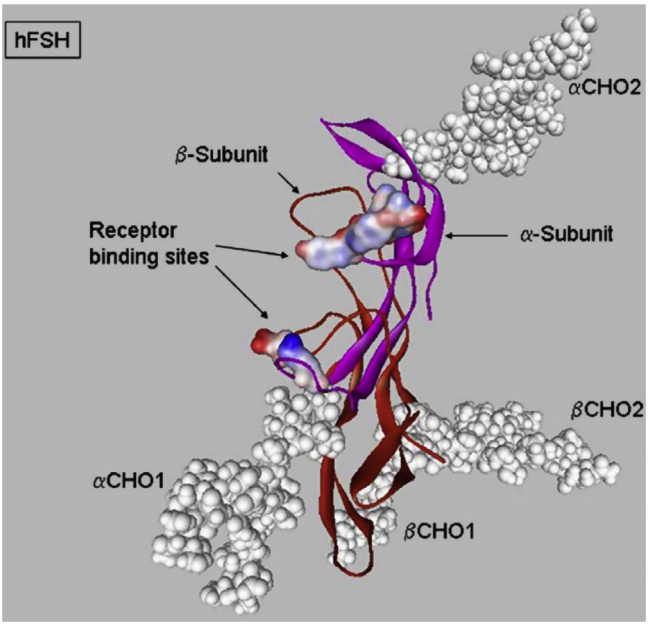

Fig. 2. Biochemical structure of human follicle-stimulating hormone (hFSH), α-subunit shown in purple, β-subunit shown in red [47].

oocyte maturation, from the germinal vesicle stage (prophase I of meiosis) to the metaphase II stage of meiosis, a process that takes approximately 36 h [56].

Medications used for controlled ovarian hyperstimulation

Since the birth Louise Brown in 1978 and with it the advent of ART including IVF [57], rates of ART use continue to rise, with more than 5 million babies born worldwide [58,59]. Whereas the birth of

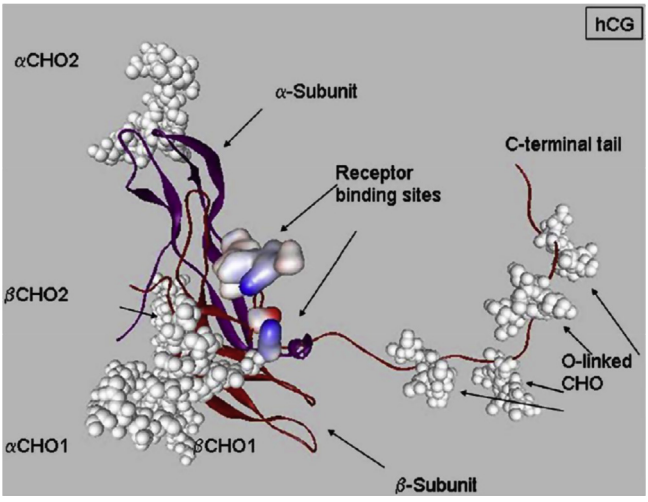

Fig. 3. Biochemical structure of human chorionic gonadotropin (hCG), α-subunit shown in purple, β-subunit shown in red [47].

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Louise Brown was achieved in a natural ovulatory cycle, the low success rates with this strategy soon led to the use of ovarian stimulation in ART, with the goal to promote synchronous growth of multiple follicles [60]. While ovarian stimulation with oral agents is possible, a more potent stimulation with higher oocyte yields can be achieved with the use of gonadotropins during COH. Given the biochemical nature of glycoproteins and to prevent digestion by stomach acid, gonadotropins are administered in injectable form.

A variety of LH and FSH preparations are available for COH, and their use differs between countries. Human menopausal gonadotropins, highly purified urinary FSH preparations, and recombinant FSH preparations are amongst the most commonly used preparations for COH [47]. Different IVF protocols exist and are based on the same principles: treatment consists of pituitary down-regulation with synchronization of a cohort of ovarian anthral follicles, controlled follicular hyperstimulation, prevention of premature endogenous ovulation, and a precisely timed trigger of ovulation with induction of final oocyte maturation approximately 36 h prior to egg retrieval.

While the pituitary down-regulation in the traditional “long protocol” was customarily achieved using a GnRH agonist, more and more commonly protocol based on GnRH antagonist is used. In this protocol, the patient may use a progestin or oral contraceptives for a brief period prior to COH in order to synchronize the current cohort of follicles, or COH may be started without pre-treatment. Premature ovulation is prevented with the use of a GnRH antagonist during the final portion of COH. Whereas FSH alone is capable of achieving follicular maturation during COH, there is some evidence that the use of a combination of LH and FSH for COH is associated with higher live birth rates than those achieved with COH using FSH alone [61].

Adjuvant medications for ovarian stimulation

Many different adjuvant medications have been advocated for ovarian stimulation, both in the setting of ovulation induction and during COH.

Glucocorticoids have been proposed as adjuvant treatment during COH in order to improve folliculogenesis and pregnancy rates. A recent Cochrane meta-analysis of eligible randomized controlled trials comparing glucocorticoid supplementation during IVF stimulation versus placebo found insufficient evidence to determine whether there was any difference between the groups in live birth rate (OR 1.08, 95% CI 0.45 to 2.58; 2 RCTs, n = 212, I (2) = 0%, low-quality evidence) [62]. The authors concluded that the safety and effectiveness of glucocorticoid administration in women undergoing COH is “unclear due to the small number of studies and low event rates”.

Recently adjuvant therapy with androgens during ovarian stimulation has come into focus. In premenopausal women, serum testosterone concentrations decrease with age [63] and parallels the decrease in ovarian reserve with increasing age as measured by levels of antimüllerian hormone (AMH) and ultrasound determinations of antral follicle count (AFC). Ovarian testosterone increases the response of antral follicles to stimulation [64], mediated or potentiated by insulin-like growth hormone I (IGF-I). In subhuman primate models, systemic Testosterone administration led to increases in preantral and antral follicles [65]. This led to the investigation of the clinical use of adjuvant androgen supplementation during ovarian stimulation to enhance oocyte yield, particularly in older reproductive-age women. A study by Balasch et al. found in a prospective pilot study that pretreatment with transdermal testosterone may improve ovarian response to gonadotrophins in poor-responder IVF patients with normal basal concentrations of FSH, however the study did not have a control arm [66]. In this study, patients only received 5 days of transdermal T, which led to increased IGF-I levels for more than a week after discontinuation. Subsequent studies employed lower amounts of T via transdermal route for longer durations, with a T pretreatment period of at least 3 weeks [67]. In one prospective randomized controlled trial on 110 low responders by Kim et al. the numbers of oocytes retrieved, mature oocytes, fertilized oocytes, and good-quality embryos, as well as embryonic implantation rate and clinical pregnancy rate per cycle initiated were significantly higher in the transdermal testosterone gel (TTG) pretreatment group [67]. The authors concluded that TTG pretreatment might be beneficial in improving both response to COS and IVF outcome in low responders undergoing IVF/ICSI. In a prior trial with a similar design, no significant beneficial effects of androgen administration on the ovarian response to FSH could be demonstrated [68]. However, the number of patients in

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that trial (n = 49), the length of duration and the transdermal gel dosage were all lower than in the subsequent study by Kim et al. Further research is needed to determine the effects of androgen pre-treatment in poor responders on ART outcomes.

In-vitro, animal and clinical studies have been conducted to investigate the relationship between ovarian aging and function of the mitochondria, which are strictly maternally inherited [69]. In particular, the role of the mitochondrial nutrient Co-enzyme Q10 (CoQ10) has been investigated. In animal studies, inhibition of murine CoQ10 synthesis caused premature ovarian insufficiency, and conversely, the age-related decline in oocyte quality and quantity could be reversed with CoQ10 supplementation [70]. In a human randomized study on 39 patients 35–43 years of age undergoing IVF-ICSI patients treated with either 600 mg of CoQ10 or placebo, the post-meiotic aneuploidy rate determined by polar body biopsy was 46.5% in the CoQ10 group compared to 62.8% in the control group [71], with clinical pregnancy rates of 33% for the CoQ10 group and 26.7% for the control group. The study was underpowered to detect significant differences in outcomes.

Further research into these and other adjuvant therapies and supplements, including DHEA, omega-3 fatty acids and antioxidants, is ongoing to better guide clinicians and patients in this context. Currently these supplements are all considered experimental.

Novel compounds

Novel compounds to stimulate ovarian function represent a major area of ongoing investigation. Considerable attention in this context is given to compounds targeting the hypothalamic KISS1 system. Since Knobil's discoveries regarding the regulation of the hypothalamic-pituitary-ovarian (HPO) axis [18,72], scientists have attempted to elucidate regulatory factors that govern GnRH secretion. Kisspeptins, a family of different sized peptides encoded by the Kiss1 gene, have emerged as upstream regulators [73,74] Genetic studies in families with idiopathic hypogonadotropin hypogonadism (iHH) provided initial evidence on the importance on the KISS1 system, identifying causal mutations in the GPR54 gene which encodes for the G-protein coupled Kisspeptin receptor [75]. Furthermore, the iHH phenotype could be reproduced in knockout mice for GPR54 or KISS1 [76]. Amongst a variety of inhibitory and excitatory regulators, kisspeptins are currently considered the most potent stimulators of GnRH secretion [77]. The discovery of the KISS1 system opens up potential avenues for treatment of major reproductive disorders such as polycystic ovary syndrome and iHH. In COH protocols as part of ART cycles, Kisspeptin may be used instead of hCG or GnRH agonists for ovulation induction ("kisspeptin trigger"), in order to reduce earl onset iatrogenic ovarian hyperstimulation syndrome (OHSS) [78].

The search for orally active gonadotropins has been extensive, without success to date. Elagolix, an oral GnRH antagonist, has been studied for the treatment of endometriosis-associated pain [79], and multi-center studies on its use for the management of heavy menstrual bleeding associated with uterine fibroids are ongoing [80]. It is feasible that this oral medication could be used instead of injectable GnRH antagonists as part of future ovarian stimulation protocols during COH.

A long-acting FSH preparation (corifollitropin alfa), given as a weekly injection in a medium dose was found to be as safe and effective as daily FSH injections for COH in women undergoing ART [81]. In another recent study, individualized dosing of a novel gonadotropin, follitropin delta, was compared with conventional dosing of follitropin alfa in a randomized noninferiority trial (ESTHER-1) [82]. The investigators found that while ongoing pregnancy (30.7% vs. 31.6%) and live birth rates (29.8% vs. 30.7%) were similar between the groups, more women in the individualized follitropin delta group had the target response of 8–14 oocytes retrieved, and fewer measures had to be taken to prevent ovarian hyperstimulation syndrome in this group (2.3% vs. 4.5%, $p < 0.01$).

A variety of ovarian stimulation protocols exist, and research is ongoing into alternatives to high-dose gonadotropin stimulation such as minimal stimulation protocols [83]. Ultimately, ovarian stimulation as part of ART protocols should be individualized based on patient characteristics such as age and ovarian reserve, and prior response to stimulation. In the future, pharmacogenomics may assist in the choice of ovarian stimulation for patients undergoing IVF [84], although success in the search for genomic predictors of ovarian response has thus far been limited [85].

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Practice Points

- The mechanisms of action of medications used to stimulate the ovaries are based on the physiology of the hypothalamic-pituitary-ovarian axis
- Common ovulatory disorders include hypothalamic anovulation, polycystic ovary syndrome and ovarian insufficiency/hypergonadotropic anovulation
- Whenever possible attempts should be made to treat the underlying ovarian disorder, such as hypothyroidism or a prolactin-secreting lactotroph adenoma
- The ideal treatment for WHO I anovulation (hypothalamic amenorrhea) is pulsatile GnRH, administered via a subcutaneous pump (available in Europe but not the United States)
- The aromatase inhibitor Letrozole is superior to Clomiphene for ovulation induction in polycystic ovary syndrome, and now considered the first line therapy
- The gonadotropins LH and FSH, derived from menopausal urine or recombinant, are used for ovulation induction or as part of controlled ovarian hyperstimulation (COH) as part of assisted reproductive technology (ART) cycles
- FSH alone can produce follicular maturation, but patients with hypothalamic dysfunction require LH, and outcomes of COH in ART may be superior with mixed preparations
- Glucocorticoids, androgens and Coenzyme Q10 may be used as adjuvants for ovarian stimulation but lack proven efficacy.

Research Agenda

- The hypothalamic KISS1 system has emerged as a major target for future research into ovarian stimulation and the treatment of reproductive disorders
- The role of androgens in ovarian stimulation for poor responders requires further investigation
- Co-Enzyme Q10 is a mitochondrial nutrient that may improve outcomes of ovarian stimulation; clinical trials are ongoing
- Long-acting FSH preparations may replace daily FSH injections as part of COH in the future
- The search for orally active gonadotropin agonists is ongoing, but has thus far been unsuccessful
- Oral GnRH antagonists such as Elagolix are being investigated in the treatment of endometriosis-associated pain and leiomyomyas, and may become part of stimulation protocols in ART in the future
- Pharmacogenomics research may assist in the choice of ovarian stimulation in ART in the future

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