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Review Article

Fertility Boosters: An Overview of Drugs Used for Ovulation Induction

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Abstract

Background: Ovulation induction involves using medications to stimulate ovulation. This process typically aims to promote the growth of ovarian follicles to address conditions such as anovulation. The drugs most frequently used for this purpose include gonadotropins, human chorionic gonadotropin (hCG), luteinizing hormone (LH), human menopausal gonadotropin (hMG), clomiphene citrate (CC), aromatase inhibitors such as letrozole, and follicle-stimulating hormone (FSH). Additionally, other drugs like gonadotrophin-releasing hormone (GnRH) analogs, insulin-sensitizing agents, and GnRH are also employed in ovulation induction for their specific benefits. These treatments are known to reduce the need for gonadotropins, increase the number of preovulatory follicles, and reduce endometrial thickness, all while maintaining a neutral impact on pregnancy rate.

Methods: In this review article, we gathered comprehensive information about the aforementioned medications and their mechanism of action from 2010 to 2024, utilizing Google Scholar, PubMed, and Web of Science databases.

Results: We concluded that FSH, hMG, hCG, and dopamine agonists are the most applicable medications and are more frequently prescribed in clinics. Recombinant drugs are also more cost-effective on the market.

Conclusion: Although the existing research provides generally comforting results, there remains a need for further studies to explore potential carcinogenic effects associated with drugs that stimulate ovulation.

Keywords: Ovulation induction, Anovulation, Infertility

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Introduction

Ovulation induction is a medical strategy aimed at correcting conditions such as anovulation or oligoovulation, which prevent women from ovulating regularly. This is especially relevant for individuals suffering from disorders such as polycystic ovary syndrome. While ovulation is commonly associated with the release of oocytes from nearly mature ovarian follicles during the late follicular phase, ovulation induction may also involve the broader process of ovarian stimulation.[1] In cases where anovulation or oligoovulation is secondary to another condition, such as an endocrine disorder, addressing the primary disease can significantly enhance pregnancy and ovulation rates.[2] However, the focus here is on medical ovarian stimulation during the early to mid-follicular phase without proceeding to in vitro fertilization (IVF), with the aim of developing one or two ovulatory follicles. The primary medications used for ovulation induction include antiestrogens, which inhibit estrogen's negative feedback on the pituitary gland, thereby increasing follicle-stimulating hormone secretion.[3] Additionally, direct ovarian stimulation is achieved through the administration of follicle-stimulating hormone. While comprehensive details on ovulation induction medications are still emerging, this overview seeks to shed light on these pharmaceutical agents from a scientific perspective, enhancing the understanding of their mechanisms and applications

in fertility and ovulation process treatments. Table 1 provides an overview of medications employed in ovarian stimulation.

Aromatase Inhibitors

Letrozole

Letrozole is an aromatase inhibitor that belongs to the cytochrome P450 superfamily of hemoprotein-containing enzymes.[4] It plays a crucial role in the rate-limiting step of estrogen synthesis, specifically converting androstenedione into estrone and testosterone into estradiol (E2). This enzyme is active across various tissues such as muscle, liver, fibroblasts, ovaries, osteoblasts, placenta, fat cells, brain, and breast tissue. The third generation of aromatase inhibitors includes two nonsteroidal inhibitors, anastrozole and letrozole, as well as a steroidal inhibitor, exemestane. Both anastrozole and letrozole act as selective and reversible inhibitors of aromatase, displaying significantly greater potency than aminoglutethimide. When administered in doses between 1–5 mg, they can reduce estrogen levels by 97% to over 99%. Both anastrozole and letrozole are fully absorbed upon oral intake and have an average elimination half-life of around 45 hours (ranging from 30 to 60 hours), with metabolism primarily occurring in the liver.[5] Common side effects include gastrointestinal issues, asthenia, hot flashes, headaches, and back pain.[6]

Initial research on letrozole used dosages ranging from 2.5 mg to 7.5 mg daily for five days or a single 20 mg dose. A 2.5 mg dose parallels its role in breast cancer hormonal therapy. The five-day regimen, administered on days 3 to 7 of the menstrual cycle, is designed to ensure clearance by ovulation time, similar to clomiphene citrate (CC). Studies indicate that a daily dose of 5 mg leads to the development of more follicles compared to 2.5 mg, resulting in higher follicle counts and increased pregnancy rates.[7-9] Aromatase inhibitors represent a novel class of drugs in fertility treatments, offering benefits such as oral administration, ease of use, affordability, and minimal side effects. Letrozole, in particular, stands out for its accessibility, reduced side effects, and lower costs compared to injectable gonadotropins. Emerging data supports the use of letrozole as a potential first-line treatment for women with ovulatory disorders.

Estradiol, synthesized by the granulosa cells of the ovaries, suppresses the release of follicle-stimulating hormone (FSH) from the pituitary gland via a negative feedback mechanism. By inhibiting the conversion of androgens into estrogens, aromatase inhibitors remove this feedback inhibition on the hypothalamic-pituitary axis, leading to an increase in FSH secretion. This rise in FSH increases androgen levels within the ovary, which

Table 1. Overview of Medications Employed in Ovarian Stimulation

Medication	Medication Brand Names	Pharmaceutical Formulations	Prevalent Adverse Reactions
Metformin	Glucophage	Tablets	• Gastrointestinal issues • Lactic acid buildup • Hepatic impairment
FSH	RDT: Gonal-F (follitropin alpha), Follistim (follitropin beta) Urinary derived: Bravelle	Injection	• Higher rates of multiple births • Elevated risk of miscarriage and early labor • Breast discomfort, enlargement, or skin reactions at the site of injection • Emotional fluctuations, depressive symptoms • Moderate to severe OHSS
CC	Serophene, Clomid	Tablets	• Dense and arid mucus in the cervix • Intermittent headaches • Formation of ovarian cysts, discomfort in the pelvic area • Changes in mood
hCG	RDT: Ovidrel (Choriogonadotropin alpha) Urinary derived: Novarel, Pregnyl	Injection	• Currently, there are no documented negative consequences linked to the sole utilization of hCG.
hMG	Urinary derived: Menopur, Repronex	Injection	• Identical to that for FSH
GnRH agonists	Zoladex (Goserelin acetate) Leuprolide acetate Synarel (Nafarelin acetate)	Injection, nasal spray, injectable implant	• Frequent episodes of increased body heat and headaches • Variations in emotional state and difficulty sleeping • Reduction in vaginal moisture • Reduction in breast volume • Discomfort during sexual activity • Reduction in bone density • These symptoms manifest with prolonged usage
LH	RDT: Luveris (Lutropin aAlpha)	Injection	• Identical to that for FSH
Dopamine agonists	Dostinex (Cabergoline) Parlodel (Bromocriptine)	Tablet	• Feelings of nausea, instances of vomiting, and congestion in the nasal passages • Experiences of headaches, sensations of dizziness, and episodes of fainting
GnRH	Lutrepulse, Factrel	Injection	• Mild OHSS • Headache • Nausea • Minimal risk of multiple pregnancies
GnRH antagonists	Cetrotide (Cetrorelix Acetate) Ganirelix Acetate	Injection	• Identical to that for GnRH agonists

Note. FSH: Follicle stimulating hormone; RDT: Recombinant DNA technology; CC: Clomiphene citrate; hCG: Human chorionic gonadotropin; hMG; Human menopausal gonadotropin; GnRH: Gonadotrophin-releasing hormone; LH: Luteinizing hormone; OHSS, ovarian hyperstimulation syndrome.

enhances the ovary's responsiveness to FSH, thereby promoting the growth of ovarian follicles. This process highlights how aromatase inhibitors can be instrumental in fostering follicular development and improving reproductive outcomes.[10]

Clomiphene Citrate

CC is a nonsteroidal agent that facilitates ovulation through indirect mechanisms. It has been widely used for several decades to promote ovulation and assist in reproductive technologies. It is particularly beneficial for treating patients with polycystic ovarian syndrome (PCOS) and anovulatory disorders.[11] Clomiphene marked a significant breakthrough in reproductive health, gaining rapid acceptance for its straightforward administration and limited adverse effects. As a selective estrogen receptor modulator (SERM), it shares similarities with tamoxifen and raloxifene.[12] These medications act as competitive antagonists at estrogen receptors, exhibiting both agonistic and antagonistic properties depending on the tissue involved. CC specifically counters estrogen's negative feedback on the hypothalamus, enhancing ovarian stimulation through increased endogenous gonadotropin activity, which elevates FSH and LH levels.[13]

Administered orally, CC treatment typically begins between the third and fifth day following the onset of spontaneous or progestin-induced menstruation, starting with a 50-mg tablet taken daily for five days.[14] The dosage can vary from 50 to 250 mg/d, although dosages above 100 mg/d are not approved by the Food and Drug Administration (FDA).[15] Once ingested, CC is absorbed in the gastrointestinal tract, metabolized by the liver, and generally exhibits acceptable tolerability. The drug and its metabolites are primarily excreted through feces, with a biological half-life of approximately 5-6 days; however, metabolites can be detected in feces for up to six weeks.[16]

Transient side effects include headaches, mood swings, and visual disturbances. Extensive research indicates that CC may exhibit genotoxic, cytotoxic, embryotoxic, and teratogenic properties.[17] The exact mechanism of its general toxicity remains unclear, though alterations in cytosolic Ca++ levels and Erk phosphorylation might play roles in its genotoxic and cytotoxic effects.[18] While analyzing the carcinogenic potential of CC, no strong links were found between its use and an increased risk of ovarian, breast, lung, colorectal, cervical, or endometrial cancers, or non-Hodgkin lymphoma.[19] Although some studies suggest a correlation, the majority indicate no significant risk. However, risks appear elevated after more than six cycles of use, particularly in women who have never been pregnant. Consequently, it is recommended that the use of CC be limited to no more than six cycles. Additionally, risks for malignant melanoma and thyroid cancer were noted to increase among women treated with CC across several studies. Further animal research and clinical cohort studies are thus essential to conclusively determine the safety of this medication (Figure 1).[19,20]

Follicle Stimulating Hormone

Human FSH is a type of gonadotropin composed of two glycoprotein subunits, α and β, which are linked non-covalently. The α subunit comprises 92 amino acids, with two undergoing carbohydrate modification. Similarly, the β subunit contains 111 amino acids, with two also modified by carbohydrates.[23]

Urinary-Derived: Urofollitropin (Bravelle)

Bravelle is a highly purified form of human FSH (hFSH) derived from the urine of postmenopausal women. This purified FSH is extracted from human urine and further refined to eliminate various proteins and impurities. FSH plays a crucial role in the growth of ovarian follicles. Administered through subcutaneous injection, it is commonly used alongside human CG (hCG) to facilitate ovulation and enhance fertility. It is also employed in IVF procedures. The dosage is customized according to individual reactions, with possible increments of 75–150 IU per day every two days, up to a maximum of 450 IU per day.[24] Common side effects include abdominal or pelvic discomfort, bloating, pain, redness, or swelling at the injection site.[25] Enhanced permeability has been noted in nano-formulations containing FSH, with liposomes demonstrating improved oral bioavailability and effectiveness in rat models.[26]

Recombinant DNA Technology

Follitropin beta and alpha represent two categories of recombinant FSHs (rFSH), both delivered subcutaneously. These are generated by introducing a plasmid carrying the FSH gene into Chinese hamster ovarian cells, leading to the production and glycosylation of the protein.[27]

Follitropin Beta (Follistim, Organon)

Follistim AQ contains FSH, which is essential for stimulating the development and maturation of an egg in women whose ovaries require hormonal stimulation for full maturation.[28] A gradual increase protocol using low doses of rFSH (follitropin beta, Puregon) begins with an initial dose of 50 IU, with adjustments made weekly based on ovarian follicular response, which is actively monitored through transvaginal ultrasonography.[29] Typical side effects include headaches, stomachache, and irritation at the injection site. An initial dose of 150 to 225 IU of Follistim is recommended for at least the first four days of treatment, with subsequent adjustments based on ovarian response.[30,31]

Follitropin Alfa (Gonal F, Serono, Norwell, Mass)

A retrospective analysis of 365 IVF cycles compared 233 cycles using follitropin beta and 132 cycles using follitropin alfa following gonadotropin-releasing hormone agonist down-regulation. Both follitropin beta and follitropin alfa differ in their carbohydrate side chains from human FSH. Research suggests that the effectiveness of FSH may depend largely 7 on the levels and types of acidic isoforms

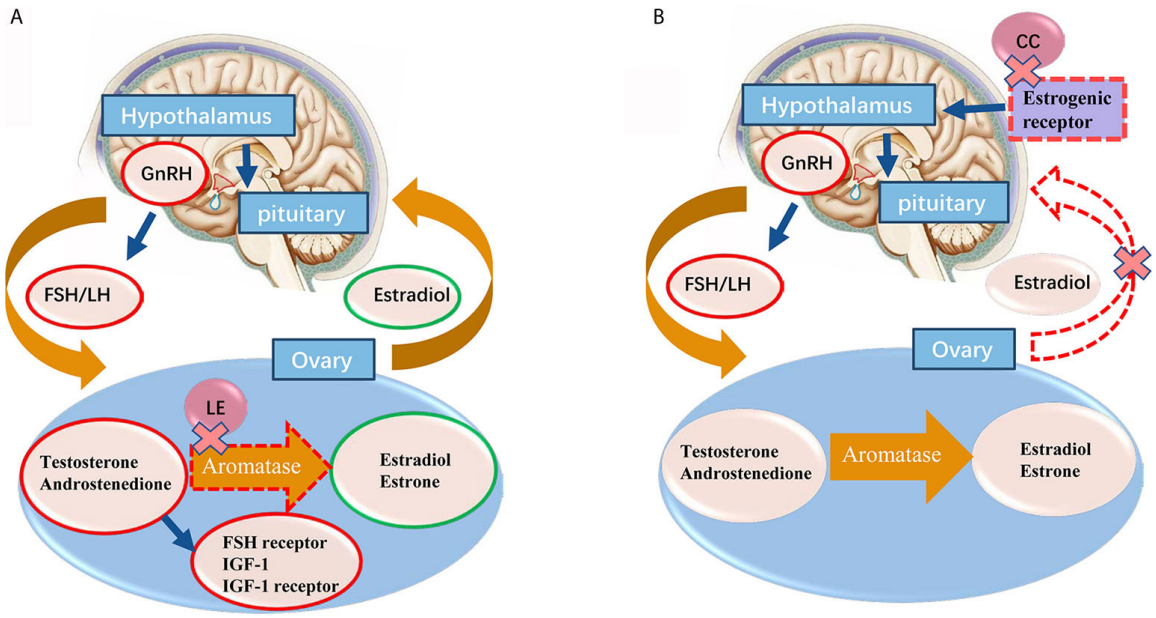

Figure 1. Letrozole's Mechanisms for Inducing Ovulation. *Note*. (A) This mechanism involves a central action that releases the pituitary-hypothalamic axis from estrogen's negative feedback, alongside a local action that inhibits the conversion of testosterone to estradiol and androstenedione to estrone within the ovary. This increases ovarian androgens, which enhances the expression of follicular FSH receptors, IGF-1, and IGF-1 receptors, thereby promoting follicular development. The normal central feedback mechanisms are preserved during the letrozole ovulation induction protocol. (B) The administration of CC stimulates gonadotropin release by attaching to estrogen receptors in the hypothalamus, which blocks the negative feedback from estradiol. A red circle indicates an increase, while a green circle indicates a decrease. In conclusion, more than half of a dose of 14C-labeled CC taken orally is eliminated within five days, yet residual radioactivity is detectable in fecal matter for up to six weeks after administration.[21] GnRH: Gonadotrophin-releasing hormone; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; IGF: Insulin-like growth factor; LE: Letrozole. Reproduced under the terms of the Creative Commons Attribution License (CC BY).[22]

present, as well as its molecular complexity. Follitropin alfa has a lower pH compared to follitropin beta, which may increase receptor affinity, extend elimination time, and more effectively stimulate folliculogenesis, as indicated in some studies. According to research by Olivennes et al, an average of 9.0 oocytes were collected, with retrieval rates across different dosage groups: 8.5 oocytes for the 75 IU group, 8.0 for the 112.5 IU group, 10.0 for the 150 IU group, 12.0 for the 187.5 IU group, and 8.0 for the 225 IU group.[32] The debate over the clinical superiority of one drug over the other continues. Previous research comparing these two forms of follitropin in terms of pregnancy and delivery outcomes has not revealed significant differences. However, no research has yet compared their effects across various age groups. A study by Williams et al found no notable differences in primary or secondary outcomes between follitropin beta and follitropin alfa, although pregnancy rates significantly declined with increasing age.[30]

Metformin

Metformin as an antihyperglycemic agent, enhances tissue responsiveness to insulin, reduces insulin levels, and suppresses glucose production in the liver. In individuals with PCOS, metformin has been found to lower levels of LH, sex hormone-binding globulin (SHBG), and ovarian androgens, while also addressing hyperinsulinemia.[33] Additionally, it promotes the restoration of regular menstrual cycles and ovulation. Nestler et al demonstrated that combining metformin with CC enhances the ovulatory response in obese women with PCOS.[34] A study examining women with PCOS divided participants into two groups: Group A, consisting of 30 women, received 1000 mg of metformin daily, while group B, also comprising 30 women, was administered 1700 mg daily. The results revealed similar ovulation rates between the two groups, with 84.8% in group A and 87.7% in group B. Additionally, the majority of participants in both groups developed a single follicle, with 91% in group A and 88.2% in group B.[35] A recent randomized study by Vandermolen et al[36] among PCOS patients further supported these findings, indicating increased pregnancy rates among anovulatory women resistant to CC treatment.

Despite these positive results, there are relatively few studies, including one small series, investigating the use of metformin alone in treating infertility. Aside from a preliminary investigation by Vandermolen et al, few studies have explored the efficacy of metformin, either alone or in combination with CC, in enhancing ovulation for the purpose of achieving pregnancy. This particular study represents the first comprehensive assessment of pregnancy outcomes in a larger cohort of anovulatory infertile women diagnosed with PCOS treated with metformin.[36]

Common side effects of metformin include nausea and abdominal pain, which were reported by 39% (19/49) of patients, but these side effects were generally transient and occurred primarily within the first two weeks of treatment.[37] Furthermore, a pilot study by Glueck et al suggested that administering metformin during pregnancy could potentially reduce the rate of spontaneous abortions in the first trimester.[38]

Research conducted by Sharpe et al, involving 4552 women, provided suggestive evidence that metformin could improve live birth outcomes when compared to a placebo. The live birth rate post-placebo was 19%, whereas the rate following metformin administration ranged from 19% to 37%. However, individuals in the metformin group were more likely to experience gastrointestinal adverse effects. Furthermore, metformin appeared to increase the rates of clinical pregnancy and ovulation.[39]

Hyperinsulinemia and hyperandrogenism (HA) play crucial roles in the pathogenesis of PCOS, and their reduction through metformin is a key aspect of the drug's beneficial impact on ovarian function in affected women. In PCOS, metformin enhances insulin sensitivity, leading to lower HOMA-IR values and a reduction in compensatory hyperinsulinemia. A potential mechanism for reducing insulin levels may involve elevating IGFBP-1 concentrations, which bind both insulin and IGF-1. Typically, IGFBP-1 expression is decreased in PCOS, but metformin therapy may help restore these levels. Hyperinsulinemia also reduces the production of SHBG, contributing to HA in PCOS. Reducing hyperinsulinemia through metformin treatment helps normalize SHBG levels, thereby preventing elevated androgen concentrations in the bloodstream.[40] Furthermore, metformin enhances the operation of the hypothalamic signaling pathway that regulates the pulsatile release of GnRH, helping to normalize elevated blood LH levels and the LH/FSH ratio commonly observed in PCOS. This decrease in LH levels reduces gonadotropin-stimulated androgen production by the ovaries.[41]

Metformin also directly influences ovarian steroidogenesis. By activating LKB1 and subsequently increasing AMPK activity, MF decreases androstenedione synthesis of androstenedione in ovarian cells, further preventing HA. It is suggested that the dominance of certain inhibitory mechanisms of metformin on HA might be linked to the specific characteristics of PCOS pathogenesis and the metabolic and hormonal status of the ovaries[42] (Figure 2).

Luteinizing Hormone

Luveris (Lutropin Alpha)

Luveris is a recombinant version of LH, which plays a crucial role in ovarian follicle growth in women. It is administered alongside follitropin alfa to address infertility in women with LH deficiency. Pharmaceutical forms of LH currently available on the market include those produced biotechnologically such as recombinant human LH (r-hLH), where the human LH gene is integrated into the genome of eukaryotic cells. Research indicates that Luveris can enhance the developmental competence of prophase bovine immature oocytes in vitro, an effect likely enhanced by FSH (Gonal-F). A study by Tarlatzis et al found that daily administration of 75 IU of LH daily is sufficient to promote normal follicular growth.[43] Additionally, LH can delay germinal vesicle breakdown, which provides valuable insights for IVF treatment protocols.[44]

Gonadotrophin-Releasing Hormone Agonists

Leuprorelin (Leuprolide Acetate)

Leuprolide, a synthetic hormone analog, is used in the management of various medical conditions, including uterine fibroids, breast cancer, and endometriosis, and as part of transgender hormone therapy.[45,46] This medication is administered either intramuscularly or subcutaneously.[47] As a GnRH analog, leuprolide reduces the levels of gonadotropins, which subsequently lowers testosterone and estradiol levels.[48]

Common side effects associated with leuprolide include hot flashes, mood instability, insomnia, headaches, and injection site pain.[49] Additional adverse reactions may include elevated blood sugar levels, allergic responses, and complications related to the pituitary gland. It is also noted that leuprolide use during pregnancy may be detrimental to fetal development.[50] Leuprolide acetate acts as a GnRH receptor agonist. Initially, it stimulates the release of pituitary gonadotropins such as LH and FSH, which subsequently increases steroidogenesis in the ovaries and testes. This leads to elevated levels of estrogen in women and dihydrotestosterone in males. However, with continuous application, leuprolide suppresses the production of LH and FSH, resulting in reduced levels of testosterone in men and estrogen in women.[51] Leuprolide acetate can be administered through injections at intervals of 1, 3, 4, or 6 months. The frequency of administration influences the required dosage, with biannual injections necessitating a higher dose compared to monthly injections. It is important to adhere to prescribed dosages, as they vary depending on the release characteristics of the formulation.[52]

Synarel (Nafarelin Acetate)

Nafarelin is a medication that acts as a GnRH agonist. It is primarily used to manage conditions such as endometriosis and precocious puberty.[53] Additionally, it is utilized to treat uterine fibroids, regulate ovarian stimulation during IVF procedures, and as a part of hormone therapy for transgender individuals.[54] The drug is administered via a nasal spray, typically two to three times daily.[55] In the treatment of PCOS, a daily dosage of 400 μg of Synarel is recommended.[56] Nafarelin works by inhibiting the production of sex hormones in the gonads, effectively reducing hormone levels by up to 95% in both males and females.[57] It also plays a role in managing uterine fibroids and is employed to regulate ovarian stimulation in IVF treatments. Furthermore, Nafarelin is effective in addressing hirsutism and PCOS by lowering gonadotropin and androgen levels.[57]

Goserelin (Zoladex)

Goserelin inhibits the synthesis of sex hormones, including testosterone and estrogen, and is particularly used in

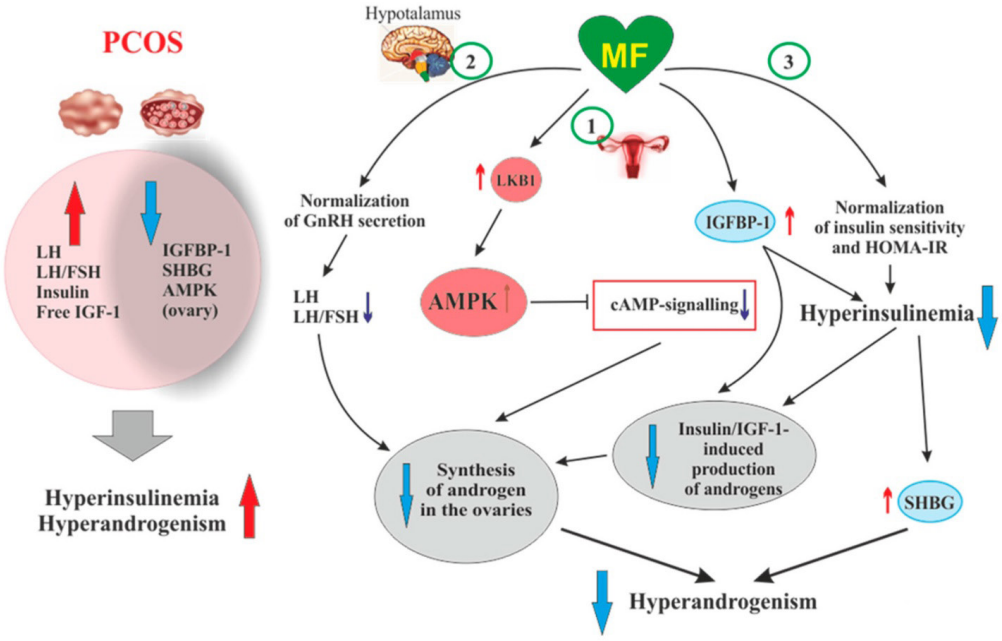

Figure 2. Metformin's Mechanisms in Mitigating Hyperandrogenism in POCS. *Note.* IGFBP-1: Insulin-like growth factor-binding protein-1; LKB1: Liver kinase B1; AMPK: AMP-activated protein kinase; SHBG: Sex hormone-binding globulin; IGF-1: Insulin-like growth factor-1; HA: Hyperandrogenism; LH: Luteinizing hormone; HOMA-IR: Homeostasis model assessment of insulin resistance; FSH: Follicle-stimulating hormone; POCS: Polycystic ovary syndrome. Reproduced under Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).[42]

the management of breast cancer.[58] In male patients diagnosed with prostate cancer and female patients with breast cancer, fibroids, endometriosis, or other non-malignant conditions linked to sex hormones, goserelin is administered as a subcutaneous injection into the front abdominal wall. This is done using a biodegradable depot that gradually releases 3.6 mg of the medication over 4 weeks.[59] Goserelin induces the secretion of testosterone and estrogen in a steady, non-fluctuating manner, which disrupts the body's natural hormonal feedback mechanisms and reduces the production of these sex hormones.[60]

Gonadotrophin-Releasing Hormone Antagonists

Recent developments in assisted reproductive technology (ART) have led to the use of GnRH antagonists during ovarian stimulation to prevent an early increase in LH.[61] Ovarian stimulation is employed in IVF to enhance success rates by promoting the growth of multiple follicles, which results in the production of numerous oocytes and embryos. Currently, the most effective treatment approach combines GnRH agonists with gonadotrophins, making it the most commonly prescribed regimen. While GnRH agonists have been shown to increase pregnancy rates, this increase is primarily attributed to the higher number of oocytes and embryos produced, rather than an improvement in embryo quality.[62]

A key benefit of using a GnRH agonist is its ability to inhibit the premature LH surge, which often leads to cycle cancellations. When implementing the long protocol, initiating GnRH agonists during the follicular or luteal phase leads to desensitization following an initial flare-up. This strategy allows for better scheduling of treatment cycles and facilitates the coordination of operations within a large IVF center. The extended protocol, which is the most frequently recommended approach, involves the administration of GnRH agonist for a prolonged period (typically 2–3 weeks) to achieve desensitization. This increases the quantity of gonadotrophin required and elevates the likelihood of ovarian hyperstimulation syndrome (OHSS). This desensitization period is associated with various side effects, including hot flashes, headaches, bleeding, and vaginal dryness.[63,64]

Ganirelix Acetate

Ganirelix acetate, known by brand names such as Orgalutran and Antagon, is an injectable GnRH antagonist.[65] Its primary use is in assisted reproductive technologies to manage the timing of ovulation. Ganirelix functions by inhibiting the effects of GnRH on the pituitary gland, leading to a rapid decrease in the secretion and activity of LH and FSH.[66] This makes it effective in preventing early ovulation during fertility treatments, ensuring that eggs mature appropriately for procedures like IVF. In contrast to GnRH agonists, which are also used in reproductive therapies and to treat conditions related to sex-steroid hormones such as endometriosis, GnRH antagonists such as Ganirelix do not cause the pituitary desensitization that results in reduced gonadotropin and sex steroid levels. This makes Ganirelix a preferred choice in certain scenarios within reproductive medicine.[67] Studies have demonstrated that the efficacy of Ganirelix in these settings is similar to that of GnRH agonists. By delaying ovulation until triggered by an injection of hCG, Ganirelix ensures the retrieval of eggs at an optimal stage of development for fertilization.

However, users of Ganirelix acetate may experience side effects such as abdominal pain, headaches, and vaginal bleeding.[68,69] The data indicates that the highest rates of viable pregnancies at 5 to 6 weeks (see Figure 1), as well as sustained pregnancies 12 to 16 weeks after embryo transfer, were observed in the group receiving 0.25 mg/day of Ganirelix, with percentages of 40.3 and 37.1 per transfer, respectively.[70,71]

Cetrotide (Cetrorelix Acetate)

Cetrorelix, marketed as Cetrotide, is a GnRH. As a synthetic decapeptide, it plays a crucial role in assisted reproductive technologies by preventing early surges of LH. The mechanism of cetrorelix involves inhibiting GnRH's effects on the pituitary gland, significantly reducing the secretion and activity of both LH and FSH.[72] Additionally, cetrorelix is used in the management of hormone-responsive cancers (e.g., prostate and breast cancers) in pre- and perimenopausal women, as well as in treating benign gynecological conditions, including endometriosis, uterine fibroids, and endometrial thinning.[73] Cetrorelix can be administered through daily subcutaneous injections of 0.25 mg or as a single 3 mg dose.[74]

Human Chorionic Gonadotropin)

As a hormone essential for recognizing pregnancy, hCG is produced by the trophoblast cells that initially surround the embryo (specifically the syncytiotrophoblast) and later contribute to the formation of the placenta following implantation.[75] The detection of hCG forms the basis of many pregnancy tests such as HCG pregnancy strip tests. Interestingly, certain malignant tumors also secrete this hormone, which can lead to elevated hCG levels in non-pregnant individuals. This can potentially indicate cancer or, in severe cases, paraneoplastic syndromes.[76] However, it remains unclear whether its production in tumors is a cause or an effect of cancer development. The pituitary gland produces LH, which occurs in both males and females of all ages. Initially secreted by the syncytiotrophoblast, beta-hCG interacts with the LHCG receptor on the ovary, supporting the corpus luteum and facilitating the secretion of progesterone during the first trimester of pregnancy.[77,78] Progesterone prepares the uterus for the developing fetus by enriching it with a dense network of blood vessels and capillaries.

It has been proposed that hCG might play a significant role in establishing maternal immunotolerance at the placental level.[79] Studies indicate that hCG treatment in endometrial cells can increase T cell apoptosis, which may foster peritrophoblastic immune tolerance and aid trophoblast invasion necessary for fetal development within the endometrium.[80] Additionally, there is evidence linking hCG levels to the severity of morning sickness or hyperemesis gravidarum in pregnant women.[81]

Due to its structural similarity to LH, hCG is also utilized clinically to trigger ovulation and stimulate testosterone production. Given its high concentration in pregnant women, urine is often collected by certain organizations to extract hCG for fertility treatments. Medications such as Varel (CG) and Pregnyl (CG) are commonly used to induce ovulation and support pregnancy in women with anovulatory infertility, provided the infertility is not caused by primary ovarian failure, following suitable pre-treatment with human menotropins.[82]

Urinary Derived: Pregnyl, Novarel

Pregnyl and Novarel are used to trigger ovulation and achieve pregnancy in women with anovulatory infertility whose anovulation is due to secondary causes rather than primary ovarian failure.[83] These women should first undergo proper pre-treatment with human menotropins. In ART, administering 10 000 IU of urinary hCG is effective in triggering the final maturation phases of oocytes.[84] Common side effects include headaches, irritability, restlessness, depression, fatigue, edema, early onset puberty, gynecomastia, and pain at the injection site.[85]

Recombinant DNA Technology: Ovidrel (Choriogonadotropin Alpha)

Ovidrel, part of a therapeutic regimen, is used to address specific fertility issues in women, typically administered alongside FSH. It provides hCG, which promotes the release of a mature egg, facilitating ovulation and increasing the likelihood of pregnancy.[86] Ovidrel is not suitable for women with primary ovarian failure, where the ovaries cannot produce eggs effectively. The findings of a study by Chang et al indicate no significant difference in the average oocyte count among treatment groups, with values of 13.6, 14.6, and 13.7 for the groups treated with 250 μg of recombinant hCG, 500 μg of recombinant hCG, and urinary hCG, respectively. However, the incidence of 2PN fertilized oocytes on the first-day post-retrieval, as well as 2PN or cleaved embryos at the time of embryo transfer, was notably higher in the group administered 500 μg of recombinant hCG compared to the group receiving the lower dose.[87] Additionally, this drug has not proven effective as a weight loss treatment and should not be used for such purposes due to the potential for severe side effects. Possible adverse reactions include redness or pain at the injection site, slight abdominal discomfort, mood fluctuations, or mild nausea and vomiting.[88]

Menotropin (Human Menopausal Gonadotropin)

Menotropin is a hormonal medication used to address fertility issues. It is commonly referred to in the plural form because it comprises a combination of gonadotropins. These menotropins are derived from the urine of postmenopausal women.[89]

Menopur

Menopur is a refined product derived from the urine of menopausal women, containing hMG with both

FSH and LH activities. It is used as an effective method for controlled ovarian stimulation (COS) in ART procedures and for the induction of ovulation in cases of anovulatory infertility.[90] It presents a distinct endocrine profile compared to rFSH, which is reflected in variations in serum levels of FSH, androgens, and estradiol. In the context of COS for women undergoing IVF or intracytoplasmic sperm injection (ICSI), Menopur has exhibited pregnancy outcomes similar to rFSH, despite yielding fewer oocytes.[91] Moreover, it has been found to enhance certain aspects of embryo quality, particularly in IVF treatments, although this effect is not observed in ICSI. When Menopur is used alongside highly purified urinary FSH, the reproductive outcomes are similar to those achieved with Menopur alone.

For cases of hypothalamic/pituitary amenorrhea and anovulation, a dosage range of 75–150 IU/day is recommended.[89] Available data on Menopur for ovulation induction remain somewhat limited, yet they indicate that ovulation rates with Menopur are comparable to those achieved with combinations of rFSH and rLH in type 1 anovulation and with rFSH alone in type 2 anovulation. Furthermore, Menopur is associated with a less pronounced follicular response and carries a lower risk of ovarian overstimulation compared to rFSH.[89]

Dopamine Agonists

Dopamine acts as a prolactin-inhibiting factor due to its ability to decrease the synthesis and release of prolactin-releasing factors via D2-like receptors. Consequently, dopamine agonists are commonly used as the first-line treatment for hyperprolactinemia.[92] Among these, ergoline derivatives such as bromocriptine and cabergoline are frequently employed. Studies have indicated that these medications effectively shrink prolactinomas by inhibiting excessive prolactin secretion, thereby restoring normal gonadal function. Elevated prolactin levels may disrupt ovulation, and by reducing prolactin, dopamine agonists such as cabergoline and bromocriptine can help normalize menstrual cycles and facilitate ovulation.[93]

Cabergoline (Dostinex)

Cabergoline, marketed as Dostinex and other brand names, is a dopaminergic medication primarily used to manage elevated prolactin levels, prolactin-secreting tumors, Parkinson's disease, and various other medical conditions. As an ergot derivative, cabergoline functions as a potent long-lasting agonist of the dopamine D2 receptor.[94] Research conducted by Shahrokh-Tehraninejad et al involving 138 women demonstrated that an oral dose of cabergoline effectively reduced the occurrence and severity of OHSS more significantly than human albumin.[95]

Bromocriptine (Parodel)

Bromocriptine, marked as Parodel, is an ergot alkaloid and dopamine receptor agonist.[96] It is the oldest dopamine agonist used for treating hyperprolactinemia. Common adverse effects include nausea, orthostatic hypotension, headaches, and vomiting, which are triggered by the activation of the brainstem's vomiting center.[97] Bromocriptine offers several benefits over cabergoline for patients susceptible to OHSS due to its shorter half-life and its extensive usage history during pregnancy. Additionally, it does not exhibit teratogenic effects; however, it may cause nausea, headaches, and orthostatic dysregulation. Moreover, bromocriptine is cost-effective, which helps reduce treatment expenses. A retrospective analysis involving 44 women at heightened risk for OHSS following ovarian stimulation for IVF demonstrated that bromocriptine, administered orally at a dose of 2.5 mg daily from the day of oocyte retrieval until all symptoms had fully resolved, prevented the development of severe, critical, or late-onset forms of OHSS.[98]

Gonadotropin-Releasing Hormone (Factrel, Lutrepulse)

Factrel (gonadorelin hydrochloride) is a compound utilized to assess the function of the hypothalamic-pituitary-gonadotropic axis. It is supplied as a sterile lyophilized powder that requires reconstitution for subcutaneous or intravenous administration.[99] The recommended dosage for adults is 100 micrograms, which can be administered via either route.[100] Common adverse reactions include headache, flushing, and nausea.[100] The release of GnRH triggers an immediate surge in LH and FSH. The episodic release pattern of LH from the pituitary gland is regulated by GnRH neurons located in the hypothalamus and the preoptic area of the forebrain.[101]

Glucagon-Like Peptide-1 Receptor Agonists

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are well-established in managing type 2 diabetes and obesity, both of which are often associated with reduced reproductive health. However, the impact of GLP-1 and GLP-1 RAs on reproductive functions remains unknown and is not thoroughly explored in clinical research. The presence of GLP-1 receptors across various parts of the reproductive system, coupled with the effects observed in preclinical models and preliminary clinical trials, suggests that GLP-1 could play a crucial role in linking reproductive and metabolic systems.

Research indicates that GLP-1 and its analogs primarily exert a stimulatory effect on mammalian reproduction, extending beyond simple weight loss. Moreover, GLP-1 is believed to possess anti-inflammatory and anti-fibrotic properties in the gonads and endometrium, particularly in conditions such as obesity, diabetes, and PCOS. Additionally, GLP-1 RAs and DPP-4 inhibitors appear to reverse polycystic ovary morphology in preclinical studies and reduce serum androgen levels and their bioavailability in women with PCOS. Early findings from clinical interventions showed that treatment with GLP-1 RAs during the preconception phase may lead

to improved menstrual regularity and higher fertility rates in overweight and/or obese women with PCOS. Current evidence suggests that using GLP-1 RAs for preconception care may offer new approaches to addressing subfertility associated with obesity, diabetes, and PCOS. Nevertheless, this relatively underexplored field warrants further investigation to answer several clinically relevant questions.[102]

Discussion

This study evaluated the effectiveness and safety of a novel, highly refined, human-sourced FSH product (Bravelle), administered either subcutaneously (s.c.) or intramuscularly (i.m.), in comparison to a recombinant FSH product (Follistim), in individuals undergoing controlled ovarian hyperstimulation (COH) for IVF-embryo transfer (IVF-ET). The findings indicate that Bravelle, whether administered s.c. or i.m., is as effective as or superior to s.c. Follistim in terms of average oocyte count, the proportion of patients undergoing oocyte retrieval, peak serum estradiol (E2) levels, pregnancy outcomes, and live birth rates. Additionally, the safety profiles were comparable across both treatment groups, with significantly less injection site pain reported in the Bravelle-administered group compared to the Follistim-treated group.[24] Two double-blind, parallel-group clinical studies (including one recently published trial) assessed a single treatment cycle of subcutaneous Bravelle versus recombinant follitropin-β (Follistim) in women with infertility undergoing IVF. The outcomes demonstrated that both Bravelle and Follistim were equally effective in inducing COH for IVF-ET, with no significant differences in the type or frequency of side effects between the two groups, although Bravelle was associated with significantly less discomfort from the injections.[103]

Research by Dhaliwal et al indicated that tamoxifen serves as an effective substitute for CC in women with PCOS and those resistant to clomiphene. Unlike CC, which has a prolonged effect due to its two-week half-life that leads to extended depletion of central estrogen receptors, aromatase inhibitors do not reduce estrogen receptor levels or negatively affect the endometrium.[104] Studies involving the use of aromatase inhibitors, primarily for women unresponsive to CC due to resistance or thin endometrium, reported positive outcomes, including ovulation rates of 70%-88%, endometrial thickness ranging from 7 mm to 9 mm, and pregnancy rates per cycle between 20% to 27%.[10] Notably, letrozole usage has been associated with enhanced endometrial conditions that are conducive to implantation and appear to yield higher pregnancy rates than CC treatments. Moreover, when combined with FSH, letrozole reduces the required FSH dose and results in the development of more mature follicles. Early findings suggest that aromatase inhibitors could enhance ovarian response in individuals who respond poorly to FSH alone.[105] An "overlapping' method was employed in this investigation. Oktay et al explored the effectiveness of tamoxifen alone or in combination with letrozole and low-dose FSH in women with breast cancer seeking embryo cryopreservation. The dual-drug protocol led to lower peak estradiol (E2) levels and yielded a higher number of embryos. The addition of letrozole to gonadotropin regimens not only decreases the required gonadotropin dose but also maintains pregnancy rates comparable to gonadotropin-only protocols.[106]

A meta-analysis examining the ovulation rates in women with PCOS treated with metformin versus CC found significantly lower ovulation rates in the metformin group compared to the CC group. Another study by Luchterhand et al showed that administering the gonadorelin hydrochloride-based GnRH salts (Factrel) generally led to fewer ovulations on Day 17 of the Double-Ovsynch protocol compared to diacetate tetrahydrate salts.[107]

Conclusion

Infertility stemming from ovulatory disorders is frequently treatable using a range of medications and therapies designed to promote the maturation and release of eggs. The drugs employed for ovulation induction may also facilitate the production of several eggs simultaneously (superovulation), which can be used alongside other procedures such as Intrauterine Insemination (IUI) and IVF to address various forms of infertility.

Ethics statement

Not applicable.

Disclosure of funding source

None.

Conflict of interests declaration

The authors declare no conflict of interests.

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Data availability statement

All data generated or analyzed during this study are included in this published article.

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Consent for publication

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