A review of the effect of fertility agents (Herbs and drugs) on the hypothalamus

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Abstract

The hypothalamus plays a central role in regulating fertility through its interactions with the hypothalamic-pituitary-gonadal (HPG) axis. This review provides a comprehensive analysis of the effects of fertility agents, including herbs and pharmaceutical drugs, on the hypothalamus and its role in fertility regulation. The hypothalamus directly influences the HPG axis by secreting GnRH, a hormone crucial for sexual development and ovulatory cycles. GnRH can be secreted in pulsatile or surge modes, with distinct implications for reproductive function. The HPG axis further regulates reproductive organs and hormonal production, affecting processes like oocyte maturation, ovulation, and steroid hormone synthesis. Herbal remedies have been used historically in various cultures to address fertility issues. Several plants, such as *Withania somnifera*, *Punica granatum*, *Camellia sinensis*, *Matricaria chamomilla*, *Vitex agnus-castus*, and *Nigella sativa*, have been studied for their potential to enhance fertility by modulating the HPG axis and influencing sex hormone levels. Pharmaceutical fertility drugs like clomiphene citrate and metformin also have a significant impact on the hypothalamus. Clomiphene citrate acts as a partial estrogen agonist in the hypothalamus, leading to increased gonadotropin-releasing hormone (GnRH) production and subsequent elevation of gonadotropin levels. Metformin, primarily used for diabetes management, can restore ovarian function in women with polycystic ovary syndrome (PCOS) and improve pregnancy outcomes. Understanding the intricate interactions between fertility agents and the hypothalamus is crucial for developing effective treatments for infertility and optimizing reproductive health.

Keywords: Hypothalamus; Fertility Agents; Fertility Treatments; Hormones; Infertility

1. Introduction

According to the World Health Organization (WHO, 2023) the inability to conceive, carry a pregnancy to term, or infertility is a disease of the reproductive system marked by the failure to achieve a clinical pregnancy after 12 months or more of regular unprotected sexual interaction. It's still a sizable problem on a global scale. The difficulties brought on by infertility are numerous and are frequently attributed to a multifaceted issue in Sub-Saharan Africa such as unsafe abortions, sexual transmitted diseases and postpartum infections (Gerrits & Shaw, 2010). The prevalence of problems with reproductive health is rising in this area (Larsen, 2000).

One major hurdle is accurately determining the prevalence of infertility. This challenge arises due to several factors. Firstly, there is diversity in how infertility is described or defined, leading to variations in what is considered infertility (WHO, 2023; Gurunath et al., 2011). Secondly, the estimates of infertility can differ based on the size of the population and the scope of coverage, whether derived from population surveys or epidemiological studies, and this discrepancy exists in low, middle, and high-income countries (Polis et al., 2017). Lastly, determining the direct causal factors or who is responsible for infertility, whether it’s males, females, or couples, adds another layer of complexity to estimating its prevalence (Gurunath et al., 2011).

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Despite the challenges in pinpointing the exact prevalence of infertility, a recent estimate published by the World Health Organisation suggests that approximately 17.5% of the global adult population, or 1 in 6 individuals worldwide, will experience infertility at some point in their lives (WHO, 2023). Breakdowns of these estimates indicate that the lifetime prevalence of infertility is approximately 17.8% in high-income countries and 16.5% in low- and middle-income countries (WHO, 2023).

Various factors affecting reproductive health have been extensively studied, but one aspect that is often overlooked is the potential impact of drugs and, to some extent, herbal remedies on fertility (Jarow et al., 2010). As noted by Jarow et al. (2010), it is crucial to investigate the role of drug-induced infertility, as some medications may have adverse effects on fertility.

In Sub-Saharan Africa, particularly in Nigeria, the use and sometimes misuse of herbal remedies are prevalent (Li et al., 2020). Nigeria’s diverse ethnic makeup (Adebawale, 2019) results in various herbal mixtures and so will herbal recommendations be specific to each ethnic group (Okaiyeto & Oguntibeju, 2021). Given this complexity, it becomes imperative to review available information regarding the hypothalamus in relation to fertility and reproduction.

This review aims to compile and discuss the effects of different exogenous fertility agents, including both herbal remedies and pharmaceutical drugs, on the hypothalamus. The hypothalamus plays a central role in regulating reproductive processes (Whirledge & Cidlowski, 2017), and understanding how these agents may influence its function can provide valuable insights into their potential impact on fertility and reproductive health.

There are several factors that have the potential of altering the function of the hypothalamic-pituitary-gonadal axis; these factors include lifestyle factors such as smoking, diets, anxiety, alcohol, drugs misuse and risky sexual behaviours arising in infections, radiation (Emokpae & Chima, 2018; Adewumi, 2017; Acharya & Gowda, 2017). Infertile have also been reported to result from abnormalities in the pituitary-gonadal axis, this has been reported in Nigerian men (Ozoemena et al., 2011).

2. The Hypothalamus: A Key Player in Fertility

2.1. HPA and HPG Axis

A sophisticated hormonal feedback mechanism that controls reproductive functions is known as the HPG axis (Speroff et al., 2012). It involves the hypothalamus, pituitary, and gonads (male testes and female ovaries, respectively). The pituitary gland is stimulated to release follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the brain, which releases gonadotropin-releasing hormone (GnRH). In turn, FSH and LH stimulate the ovaries to create testosterone in men and estrogen and progesterone in females (Hall & Hall, 2020).

The hypothalamic-pituitary-adrenal axis (HPA) and the hypothalamic-pituitary-gonadal axis (HPG) are important endocrine systems that play key roles in controlling a variety of physiological processes, including stress response and regulation (Sapolsky, 2015; Handa & Weiser, 2014). Over the course of nearly six decades, a great deal of research has been done on how the HPA and HPG axes interact. The underlying biological contexts that establish links between these two axes, as well as the complex interactions involving particular sex hormones and their metabolites with the HPA axis, have all been studied in detail in systematic meta-analyses and thorough reviews (Handa & Weiser, 2014; Chrousos, 2009).

As the primary regulator of the body’s reaction to stress, the HPA axis plays a key role (Nestler & Duman, 2012). The hypothalamic-pituitary-adrenal (HPA) axis, which consists of the hypothalamus, pituitary, and adrenal glands, directs the body’s adaptive response to stressors (Smith, 2006). The paraventricular nucleus (PVN) of the hypothalamus contains neurons that release arginine vasopressin (AVP) and corticotropin-releasing hormone (CRH) in response to the activation of the HPA axis. The anterior pituitary gland is induced by these neuropeptides to release adrenocorticotropic hormone (ACTH) (Stephens & Wand, 2012). In response, ACTH stimulates the production and release of glucocorticoids (cortisol in humans and corticosterone in rodents), mineralocorticoids (aldosterone), and adrenal androgens. These substances are then released from the adrenal cortex into the bloodstream (Stephens & Wand, 2012).

The hypothalamic-adrenal-gonadal (HPG) axis, which controls the maturation of reproductive organs and reproductive competence, is influenced by the HPA axis (Whirledge & Cidlowski, 2017). Gonadotropin-releasing hormone (GnRH), which is first secreted by the hypothalamus, is the first endocrine signal used by the HPA axis to control the reproductive system. In order to produce and release follicle-stimulating hormone (FSH) and luteinizing hormone (LH), GnRH...
stimulates the pituitary’s gonadotroph cells (Whirledge & Cidlowski, 2017; Namwanje & Brown, 2016). Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) then influence the ovaries to control procedures like oocyte maturation, ovulation, and the production of steroid hormones (Richards & Pangas, 2010). Activins, inhibins, and the estradiol and progesterone produced by the ovaries all contribute to feedback mechanisms that regulate the secretion of gonadotropins (Namwanje & Brown, 2016). According to reports, elevated glucocorticoid levels have inhibitory effects on GnRH neurons, pituitary gonadotrophs, and the gonads (Whirledge & Cidlowski, 2017).

2.2. Function of the hypothalamus in the reproductive system.

The hypothalamus plays an important role in the production of reproductive hormones such as gonadotrophin-releasing hormone (GnRH), which stimulates the production and release of FSH and LH (Gabriela et al., 2018; Whirledge & Cidlowski, 2017; Namwanje & Brown, 2016).

2.2.1. Secretion of GnRH

The GnRH is a critical hormone in the hypothalamic-pituitary-gonadal axis (HPG) in humans and is produced in hypothalamic neurons; the hormone governs sexual development in humans from adolescence through ovulatory cycles in women (Casteel & Singh, 2023).

Pulsatile and surge forms of GnRH secretion have been described (Maeda et al., 2010).

Pulsatile Secretion of GnRH

GnRH is episodically released in discrete pulses into the portal circulation during pulsatile secretion. Notably, there are intervals of undetectable GnRH concentrations between these pulses (Maeda et al., 2010; Moenter et al., 2003).

The hypothalamic level is where neurosecretory cells synthesize and periodically release GnRH into the hypothalamus-hypophysial-portal circulation (Marques et al., 2022). In reaction, anterior pituitary gonadotropes synthesize and release the gonadotropins, FSH and LH. These hormones jointly exert control over gonadal activity (Klein, 2003).

In the case of women, FSH stimulates the growth and maturity of ovarian follicles, whereas LH causes ovulation and the creation of the corpus luteum (Klein, 2003). In men, on the other hand, FSH initiates spermatogenesis and, in conjunction with higher intratesticular testosterone levels, maintains this critical process. Meanwhile, LH regulates androgen synthesis in the testes via the Leydig cells (Klein, 2003).

Surge Secretion of GnRH

The surge form of GnRH production is found in females, particularly during the pre-ovulatory phase, where there appears to be a constant presence of GnRH in the portal circulation (Maeda et al., 2010; Moenter et al., 2003).

3. Effect of Fertility Agents on the HPG Axis

A compromised functioning of the hypothalamic-pituitary-gonadal (HPG) axis can lead to a diverse range of reproductive disorders, including some that are inherited, acquired, or of uncertain origin. One prevalent clinical consequence arising from HPG dysfunction is infertility (Acosta-Martínez, 2023).

3.1. Herbs and Their Effects on the Hypothalamus

Herbal medicines and formulations have served as remedies for infertility since ancient times, with a rich historical legacy (Petrovska, 2012). The roots of herbal medicine can be traced back to prehistoric eras, and written records from ancient China and Egypt, dating as far back as 3,000 BC, extensively detail the therapeutic applications of various plant-based treatments (Patwardhan et al., 2005). Indigenous cultures, including those of Africa and Native America, integrated herbs into their healing rituals, while others developed traditional medical systems like Ayurveda and Traditional Chinese Medicine, both of which incorporated herbal therapies (Xu et al., 2013; Petrovska, 2012).

In Mexico, medicinal plants have played an integral role in addressing diverse reproductive health concerns among women (Cabada-Aguirre et al., 2023). Although certain plants have undergone clinical scrutiny, a majority of the medicinal herbs employed in women’s reproductive health lack rigorous scientific validation (Cabada-Aguirre et al., 2023).
A contemporary trend involves the utilization of isolated natural compounds or crude plant extracts to tackle male infertility challenges, encompassing issues such as low sperm count, sexual asthenia, and erectile dysfunction, as well as addressing female reproductive complexities including menstrual disorders, ovulation disorders, and fallopian tube blockages (Jaradat & Zaid, 2019).

In North America, botanical remedies were widely deployed for fertility enhancement, spanning from colonial times up until 1900, and current discussions explore their potential integration with modern infertility treatments (Lans et al., 2018).

Infertility is a prevalent issue in Africa, including Nigeria, leading many individuals to turn to herbal remedies for treatment (Subair & Ade-Ademilua, 2022). Subair and Ade-Ademilua (2022) documented the utilization of several plants for addressing female infertility in Nigeria. Their research highlights the use of specific plants, such as *Momordica charantia* L. (commonly referred to as Ejinrin-wewe by the Yorubas), *Ocimum gratissimum* L. (Efinrin), *Vernonia amygdalina* Del. (Ewuro), and *Tragia benthamii* (Esinsin funfun), as well as others like *Pistia stratiotes* L. (Oju-oru), *Cocus nucifera* L. (Agbon), and *Euphorbia hirta* L. (Ege-gogoro), among others. These plants are often prepared by distillation in local spirits or used in aqueous preparations as traditional remedies for infertility in Nigeria.

Herbal remedies are universally recognized as one of the most accessible avenues for addressing infertility (Jaradat & Zaid, 2019), a condition laden with profound personal, social, and psychological ramifications (WHO, 2023). Notably, infertility affects both males and females in a relatively equitable manner (Jaradat & Zaid, 2019).

Several studies have outlined several plants used for fertility treatments and the ability to increase fertility by amplifying the hypothalamic–pituitary–gonadal axis (Akbaribazm et al., 2020; Ye & Shaw, 2020; Abdnejad & Simbar, 2016).

3.1.1. *Withania somnifera*

In various African nations, *Withania somnifera*, also known as Ashwagandha, can be found growing naturally, including countries such as Nigeria, South Africa, Lesotho, Sudan, South Sudan, Djibouti, Egypt, Tanzania, Swaziland, Mali, Liberia, and Congo (Naveen et al., 2015). This plant is particularly recognized as indigenous to South Africa, where it is frequently employed for its sedative and hypnotic properties. Additionally, it is esteemed for its efficacy in addressing a wide range of health issues within the southern African region (Naveen et al., 2015).

*Withania somnifera* has been prescribed in traditional medicine for a wide range of health conditions, including the management of premature ejaculation, polyarthritis, painful swellings, lumbago, oligospermia, vitiligo, general debility, ulcers, including infertility, inflammation of the uterus, vaginal discharge, and inflammation of the testes (Ali et al., 2017).

Studying *Withania somnifera* extract through LC-ESI/MS, Nasimi et al. (2018) confirmed the presence of various compounds, such as anafener, anahygrine, hygrine, cuscohygrine, tropine, pseudotropine, withananine, pseudowithanine, somnin, and somniferine-3-tropyltigloate, with most of these compounds falling under the category of polyphenols, including isoflavones and flavonoids, which can exert estrogenic effects.

In a study conducted by Saiyed et al. (2016) involving rats with letrozole-induced polycystic ovarian syndrome, it was observed that the serum levels of LH decreased, while FSH levels increased. Furthermore, there was a reduction in preantral and antral follicles as well as corpus luteum compared to the control group over a 22-day period (Saiyed et al., 2016).

In another study by Bhattarai et al. (2010), it was found that Ashwagandha extract, through its GABA mimetic properties, led to increased secretion of gonadotropin hormones and ultimately improved oogenesis. According to Bhattarai and colleagues, this improvement was attributed to the enhancement of the HPG axis and the restoration of serum estrogen balance.

3.1.2. *Punica granatum*

*Punica granatum*, commonly referred to as pomegranate, belongs to the Punicaceae family and is indigenous to various regions across the globe, including northern India, Iran, Turkmenistan, the Middle East, and the Mediterranean (Holland et al., 2009).
Pomegranate is characterized by its high-water content and abundant supply of essential nutrients, including vitamin C and various polyphenols such as anthocyanins, punicalagin, ellagic acid, and gallic acid. Within pomegranate seeds, phytoestrogens like genistein, daidzein, coumestrol, as well as glutamic and aspartic acids are also present (Battineni et al., 2017).

An animal study conducted on rats with polycystic ovary syndrome (PCOS) demonstrated that pomegranate extract, attributed to its phytoestrogen content, has the capacity to regulate and alleviate PCOS symptoms (Hossein et al., 2015). The extract's mechanisms of action include the enhancement of mucus secretion through increased uterine blood flow (vasodilatation) and the augmentation of uterine wall thickness. These changes in mucosal secretions, facilitated by anti-inflammatory mechanisms, contributed to an enhanced implantation rate (Hossein et al., 2015).

Salau et al. (2023) conducted a study in which testicular oxidative injury was induced by incubating testes tissues in a mixture of Krebs buffer and FeSO₄·7H₂O solution. This induction led to decreased levels of reduced glutathione, glycogen, total cholesterol, triglyceride, and HDL-cholesterol, as well as a decrease in the activities of superoxide dismutase, catalase, ENTPDase, and 5′Nucleotidase. Moreover, it resulted in a distorted testicular histological architecture. Salau and colleagues (2023) supplied, however, that treatment with pomegranate fruit extract significantly reversed these alterations in levels and activities while preserving the normal testicular morphology.

Metabolite analysis revealed changes in specific compounds, including octadecenoic acid, 1,2,3-propanetriyl ester, ((E,E,E); squalene; cholesterol; 6-Octadecenoic acid, (Z); (ZZ)-2-Octenoic acid; methyl tetradecanoate; methyl 14-methylpentadecanoate; octadecanoic acid, 2-{[(1-oxohexadecyl)oxy]ethyl ester (Salau et al., 2023). These changes were accompanied by alterations in alpha linolenic acid and linoleic acid metabolism, as well as steroidogenesis (Salau et al., 2023). Notably, treatment with pomegranate extract ameliorated the levels of oxidative-generated metabolites and concurrently restored arachidonic acid, cholesterol margranate, ethyl lithocholate, and reactivated the previously inactivated metabolic pathways (Salau et al., 2023).

3.1.3. Camellia sinensis

Camellia sinensis extract has been demonstrated to exert a protective effect against induced reproductive toxicities and a reduction in testicular androgen receptors (Abdelrazek et al., 2016). Additionally, it effectively mitigates induced damage to the reproductive system, primarily attributed to its high catechins content (Zanchi et al., 2015). Catechins are known for their ability to counteract reactive oxygen species, which lead to oxidative stress in both male and female reproductive systems, potentially causing infertility (Roychoudhury et al., 2017). Moreover, epigallocatechin gallate (EGCG), a prominent component of Camellia sinensis, have been reported to enhance the overall efficiency of fertilization by improving the penetration rate of sperm in vitro (Gadani et al., 2017).

In animal study, Khodarahmi et al. (2020) induced PCOS in female Wistar rats using letrozole. Their study revealed that Camellia sinensis restored and regulated the secretion and concentration of sex hormones including testosterone, LH, estradiol and FSH. They attributed this activity to the antioxidant and phytoestrogenic properties of Camellia sinensis (Khodarahmi et al., 2020). This effect is particularly significant because the aromatase enzyme, involved in estradiol synthesis in ovarian granulosa cells, is inhibited by the isoflavones present in green tea, leading to a dose-dependent reduction in estradiol production by these granulosa cells (Morshed et al., 2016).

Additionally, another study indicated that the extract of Camellia sinensis, administered in a dose-dependent manner (100, 200, and 400 mg/kg for 15 days), enhanced the maturity and secretory activity of mammary sinuses by regulating prolactin secretion (Al-Snafi et al., 2015).

3.1.4. Matricaria chamomilla

In a study investigating the impact of Matricaria chamomilla extract on the growth and maturation of isolated mouse ovarian follicles within a three-dimensional culture system, Shoorei et al. (2018) demonstrated several notable effects (Kesmati et al., 2007). The extract was found to elevate levels of progesterone, 17β-estradiol, and dehydroepiandrosterone in the culture medium while concurrently reducing levels of reactive oxygen species (ROS). Additionally, it resulted in decreased follicular diameter and antrum formation, ultimately extending the survival of oocytes (Shoorei et al., 2018).

Kesmati et al. (2006) studied gonadectomized mice, and revealed that chamomile extract had a positive influence on estrogen-dependent sexual parameters such as hair growth, temperature fluctuations, and menstrual cycle regulation.
Furthermore, Gholami et al. (2016) conducted a double-blinded clinical trial involving 80 post-term pregnant women with a gestational age of 40 weeks or more. Their findings indicated that, after one week of consuming capsules containing chamomile extract, labour symptoms began to manifest. In comparison to the control group, the chamomile extract group experienced a decrease in both labour pain and contraction duration.

Silva et al. (2018) studied the galactogogue effects of chamomile’s phytoestrogenic compounds by elucidating their mechanism of action on dopamine receptors. Their human studies revealed that chamomile extract had the capacity to enhance lactogenesis in lactating women.

3.1.5. *Vitex Agnus-castus*

According to Askari (2017), the *Vitex Agnus-castus* extract possess the ability to stimulate the secretion of the corpus luteum post-ovulation, thereby promoting the production of progesterone. This progesterone production plays a pivotal role in regulating the female sexual cycle (Askari, 2017).

In an animal study conducted by Yakubu and Akanji (2011), it was observed that the group administered with Verbenaceae extract exhibited increased serum levels of estrogen and progesterone compared to the control group. Simultaneously, levels of LH and prolactin, hormones known to disrupt sexual function, decreased in this group.

Furthermore, research on rats with induced PCOS revealed significant effects of the plant extract. Jelodar & Karami (2013) noted that after 28 days, the extract led to a reduction in the number of preantral and antral follicles as well as corpus luteum compared to the control group. Additionally, the diameter of antral follicles and the thicknesses of follicular theca and ovarian tunica albuginea increased in comparison to the control group.

3.1.6. *Nigella sativa*

There are evidence that the extract derived from *Nigella sativa*, owing to its rich content of phytoestrogenic and flavonoid compounds, is effective in reducing ovarian cyst formation induced by exposure to estradiol valerate, letrozole, and dehydroepiandrosterone in diverse animal models used to simulate PCOS (Khani et al., 2021; Eini et al., 2020).

*Nigella sativa* extract has been proposed to ameliorate PCOS through multiple mechanisms, including the upregulation of mRNA expression associated with epigenetic factors (Dnmt1 and Hdac1), maternally derived genes (Mapk and Cdk1), the reduction of reactive oxygen species (ROS), and modulation of the hypothalamic-pituitary-gonadal (HPG) axis. Specifically, it exerts its effects by suppressing luteinizing hormone (LH) and estrogen secretion while simultaneously enhancing follicle-stimulating hormone (FSH) levels (Khani et al., 2021).

The long-term utilization of *N. sativa* extract, primarily due to its phytoestrogen content, has the capacity to decrease testosterone levels, initiating a negative feedback loop on LH production. Consequently, reduced androgen levels may lead to a diminished predominance of LH over FSH. Furthermore, it is hypothesized that *Nigella sativa* extract may mitigate LH dominance over FSH by inhibiting nitric oxide and leptin-releasing neurons, which are directly involved in the synthesis of LH within the anterior pituitary gland. This multifaceted action potentially enhances ovulation in women afflicted with PCOS (Eini et al., 2020).

3.2. **Pharmaceutical Fertility Drugs/Treatments and the Hypothalamus**

Pharmaceutical fertility medications are incredibly important for helping people or couples who are having fertility problems get pregnant (Balen, 2019; Kamel, 2013). The hypothalamus, which is crucial in controlling the menstrual cycle and fertility, is one of the reproductive system's many organs that these medications frequently target (Speroff et al., 2012).

3.2.1. **Clomiphene citrate (Clomid)**

Commonly prescribed fertility medication clomiphene citrate affects the brain and pituitary (Tulandi & Martin, 2013). It functions by obstructing estrogen receptors in the hypothalamus, increasing the generation of GnRH. The pituitary gland is then stimulated to release more FSH and LH, which can improve ovulation in women with ovulatory problems (Thomson & Kalra, 2008).

Clomiphene exhibits selective binding to estrogen receptors in various tissues, including the hypothalamus, ovary, endometrium, and cervix, resulting in both estrogenic and anti-estrogenic effects (Mbi Feh & Wadhwa, 2022). Notably,
in the hypothalamus, it acts as a partial estrogen agonist, initiating an estrogenic negative feedback mechanism. Consequently, this leads to an increase in gonadotropins (Mbi Feh & Wadhwa, 2022).

Research conducted by Huijben et al. (2022), Herzog et al. (2020), and Kettel et al. (1993) indicated that clomiphene citrate treatment effectively restores the HPG axis by elevating testosterone levels in men with low testosterone levels.

Clomiphene citrate (CC) competes with estradiol at the receptor level, specifically within the anterior hypothalamus and hypophysis, thereby blocking the negative feedback mechanism and resulting in increased GnRH production. Clomiphene citrate, characterized by a half-life of 5 days, consists of two compounds: 38% of zuclomiphene (cis-isomer) and 62% of enclomiphene, both of which are excreted through the intestines (Dickey & Holtkamp, 1996).

Zuclomiphene exhibits characteristics of both a partial estrogen agonist and antagonist, while enclomiphene is purely antiestrogenic. Unlike testosterone, neither of these compounds suppresses the HPG axis; instead, they lead to an increase in LH and FSH, promoting the production of intratesticular testosterone by the Leydig cells and fostering spermatogenesis (Paulson & Wacksman, 1976).

Kettel et al. (1993) documented that clomiphene citrate-induced ovulation in women with PCOS is accompanied by heightened secretion of LH and FSH, along with increased estrogen levels. This increased LH pulse amplitude following CC, coupled with decreased pituitary sensitivity to GnRH, indicates a hypothalamic effect.

In their study on hypogonadal males, Huijben et al. (2022) explored CC as a potential alternative to testosterone therapy. Their retrospective evaluation of men treated with CC for hypogonadism revealed significant improvements in hormonal profiles, including total testosterone (TT), free testosterone (FT), LH, and FSH. During treatment, TT increased from 9 to 16 nmol/L, with 89% of patients experiencing a biochemical increase. Notably, increased TT levels persisted even after eight years of treatment, and 74% of patients reported improvement in hypogonadal symptoms.

3.2.2. Metformin

Metformin (MF), a primary medication for managing type 2 diabetes mellitus (T2DM), both as a standalone treatment or as combined therapy, has been shown to restore ovarian function in women with PCOS. Furthermore, it contributes to improved fetal development, enhanced pregnancy outcomes, and enhanced offspring health in individuals with gestational diabetes mellitus (GDM) and T2DM (Shpakov, 2021).

Recently, the utilization of MF therapy has gained widespread acceptance for addressing the metabolic and hormonal irregularities in women with PCOS and for rejuvenating their reproductive capabilities (Abdalla et al., 2020). This therapy has also demonstrated its efficacy in enhancing outcomes in in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI) procedures in PCOS patients (Bordewijk et al., 2017).

Notably, MF proves particularly effective when employed to treat PCOS patients exhibiting metabolic disturbances such as T2DM, obesity, dyslipidemia, and severe insulin resistance (IR) (Witchel et al., 2019). The efficacy of MF in this context can be attributed to its ability to mitigate the adverse effects of these conditions on female reproduction. This includes enhancing tissue sensitivity to insulin, ameliorating lipid and glucose metabolism, modulating cell metabolism, and reducing inflammation and oxidative stress, both in the ovaries and other tissues.

MF is recommended for inducing ovulation in PCOS women who either exhibit resistance to CC or require antiandrogen therapy without concurrent contraceptive use. It is also recommended for PCOS patients with severe obesity and impaired lipid metabolism (Wu et al., 2020). MF treatment for PCOS individuals has been shown to normalize the frequency and regularity of ovulation, even when administered alongside exogenous gonadotropins (Sharpe et al., 1996).

3.2.3. Combination of Letrozole and Metformin

Recent research has provided valuable insights into the efficacy of combining MF with letrozole, an aromatase inhibitor widely employed to restore ovarian cycling, induce ovulation, and enhance oocyte implantation and pregnancy rates in women with PCOS, especially those with reduced responsiveness to CC (Sawant & Bhide, 2019; Rezk et al., 2018). This combined therapy involving MF has shown significant enhancements in the positive effects of letrozole on pregnancy and live birth rates. Notably, clinical findings indicate that the combined utilization of letrozole and MF surpasses the effectiveness of the combination of CC and MF (Yu et al., 2017; Bjelica et al., 2016).
3.2.4. Agonists and antagonists of the gonadotropin-releasing hormone (GnRH)

Medication used in assisted reproductive technologies (ART), such as in vitro fertilization (IVF), includes GnRH agonists and antagonists (Lambalk et al., 2006). When the pituitary gland becomes desensitized, GnRH agonists cause the release of FSH and LH to be suppressed after first stimulating it (Al-Inany et al., 2016). On the other hand, GnRH antagonists obstruct GnRH action directly, stopping early ovulation during IVF cycles (Huîrne et al., 2005).

Examples of Inhibitors (agonists) of GnRH are i. Leuprolide (Lupron), a GnRH agonist frequently used in ART in the treatment of disorders like endometriosis and uterine fibroids (Sharpe-Timms, 1997). FSH and LH are first stimulated to be released, but when the pituitary gland becomes desensitized, they are subsequently suppressed; ii. Goserelin (Zoladex), a GnRH agonist used in situations when leuprolide is appropriate. The pituitary gland’s response to GnRH is downregulated by this medication, which is given as an implant or injection (The Goserelin Study Group, 1984); and iii. Triptorelin (Decapeptyl), used in the treatment of prostate cancer, ART, and other situations where it is necessary to reduce the pituitary’s sensitivity to GnRH (Fauser & Van Heusden, 1997).

Instances of antagonists of GnRH and their uses are i. Cetrorelix (Cetrotide), a GnRH antagonist employed to avoid early ovulation during IVF cycles. It specifically inhibits the pituitary gland's GnRH receptors from acting (Loutradis et al., 2001); ii. Ganirelix (Orgalutran), used in ART to accomplish the same goal as Cetrorelix: to prevent early ovulation (Devroey et al., 2009); and iii. Degarelix (Firmagon), used to treat advanced prostate cancer. It quickly lowers the production of testosterone by acting as a GnRH antagonist (Van Poppel et al., 2017).

3.2.5. Hypothalamic Function Suppression

Certain fertility procedures, such ovarian hyperstimulation in IVF, can momentarily impair normal hypothalamus activity (Delvigne & Rozenberg, 2002). To stop the ovaries from being overstimulated, this is carefully regulated (Youssef et al., 2010).

Ovarian Hyperstimulation in IVF

- Lupron Trigger: In some IVF cycles, the drug lupron (leuprolide) is utilized as a trigger for the final maturation of the oocyte. The hypothalamus and pituitary are initially suppressed, but at a time when LH and FSH levels need to spike for oocyte retrieval (Sönmez et al., 2008).
- Protocol for GnRH antagonists: In IVF protocols, GnRH antagonists like Cetrorelix or Ganirelix are used to regulate ovarian hyperstimulation and prevent premature ovulation. They short-term suppress hypothalamic activity (European and Middle East Orgalutran Study Group, 2001).
- GnRH Agonist Downregulation: Before ovarian stimulation in IVF, GnRH agonists like Leuprolide may be administered to first downregulate the hypothalamus and pituitary. This short-term restraint aids in regulating the timing of follicular growth (Kolibianakis et al., 2006).
- Two Triggers: In some IVF methods, it may be possible to precisely control the hypothalamic's suppression and the timing of oocyte maturation by using both an agonist (such as a GnRH agonist) and an antagonist (such as a GnRH antagonist; Humaidan et al., 2013).

4. Conclusion

In conclusion, the hypothalamus plays a pivotal role in regulating fertility through its intricate interactions with the hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis governs the production and release of crucial reproductive hormones, including GnRH, FSH, and LH, which in turn orchestrate the reproductive processes in both males and females.

The use of fertility agents, including herbs and pharmaceutical drugs, can have a significant impact on the hypothalamus and the HPG axis. Herbs like Withania somnifera, Punica granatum, Camellia sinensis, Matricaria chamomilla, Vitex Agnus-castus, and Nigella sativa have been utilized in traditional medicine to address various aspects of fertility; research suggests that they can influence the HPG axis by modulating hormone levels and promoting reproductive function.

It is evident that fertility agents can exert both positive and negative effects on the hypothalamus and the HPG axis. Understanding these effects is crucial for optimizing fertility treatments and addressing reproductive disorders effectively. As research in this field continues to evolve, it holds the potential to provide new insights into the intricate interplay between fertility agents and the hypothalamus, ultimately benefiting individuals and couples striving to achieve and maintain healthy reproductive function.
Disclosure of conflict of interest
No conflict of interest to be disclosed.

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