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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 (Adebowale, 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 HPG 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 anaferin, 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 $FeSO_4 \cdot 7H_2O$ 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)-; (2Z)-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 (Morshedi *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 medicines 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 (Huirne *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 (Sönmezer *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 hypothalamus'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.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

References

[1] Abdalla, M. A., Deshmukh, H., Atkin, S., & Sathyapalan, T. (2020). A review of therapeutic options for managing the metabolic aspects of polycystic ovary syndrome. Therapeutic Advances in Endocrinology and Metabolism, 11, 2042018820938305.

[2] Abdelrazek, H. M., Helmy, S. A., Elsayed, D. H., Ebaid, H. M., & Mohamed, R. M. (2016). Ameliorating effects of green tea extract on cadmium induced reproductive injury in male Wistar rats with respect to androgen receptors and caspase-3. Reproductive biology, 16(4), 300-308.

[3] Abdnejad, R., & Simbar, M. (2016). A review on herbal medicines effective of premenstrual syndrome in Iran. The Iranian Journal of Obstetrics, Gynecology and Infertility, 19 (11), 18–30.

[4] Acharya, S., & Gowda, C. R. (2017). Lifestyle factors associated with infertility in a rural area: a cross-sectional study. International Journal of Medical Science and Public Health, 6 (3), 502-7.

[5] Acosta-Martínez M. (2023). Hypothalamic-Pituitary-Gonadal Axis Disorders Impacting Fertility in Both Sexes and the Potential of Kisspeptin-Based Therapies to Treat Them. Handbook of experimental pharmacology, 10.1007/164_2023_666. Advance online publication. https://doi.org/10.1007/164_2023_666

[6] Adebowale A. S. (2019). Ethnic disparities in fertility and its determinants in Nigeria. Fertility research and practice, 5, 3. https://doi.org/10.1186/s40738-019-0055-y

[7] Adewumi, E. A. (2017). Infertility treatment financing in Nigeria. Nigerian Journal of Health Sciences, 17(1), 38.

[8] Akbaribazm, M., Khazaei, M. R., & Khazaei, M. (2020). Phytochemicals and antioxidant activity of alcoholic/hydroalcoholic extract of Trifolium pratense. Chinese Herbal Medicines, 12(3), 326-335.

[9] Ali, K., Shuaib, M., Ilyas, M., Hussain, F., & Hussain, F. (2017). Medicinal uses of chemical extracts from Withania somnifera and its antimicrobial activity: a mini review. PSM Microbiology, 2(1), 20-23.

[10] Al-Inany, H. G., Youssef, M. A., Aboulghar, M., & Broekmans, F. J. (2016). Gonadotrophin-releasing hormone antagonists for assisted reproductive technology. The Cochrane Database of Systematic Reviews, (4), CD001750.

[11] Al-Snafi, A. E., Khorsheed, S. H., & Farj, A. H. (2015). Mammary gland stimulating effects of the crude phenolic extracts of green tea (Camellia sinensis). International Journal of Biological & Pharmaceutical Research, 6 (7), 573-576.

[12] Askari, K. (2017). Effect of hydroalcoholic extract of Vitex agnus-castus fruit on fertility and estrous cycle in letrozole-induced polycystic ovary (PCOS) in rat. Razi Journal of Medical Sciences, 24(156), 42-48.

[13] Balen, A. H. (2019). Female infertility: causes and treatment. Journal of the Turkish German Gynecological Association, 20 (2), 69-75.

[14] Battineni, J. K., Boggula, N., & Bakshi, V. (2017). Phytochemical screening and evaluation of anti-emetic activity of Punica granatum leaves. European journal of pharmaceutical and medical research, 20017 (4), 4.

[15] Bhattarai, J. P., Ah Park, S., & Han, S. K. (2010). The methanolic extract of Withania somnifera ACTS on GABAA receptors in gonadotropin releasing hormone (GnRH) neurons in mice. Phytotherapy Research, 24(8), 1147-1150.

[16] Bjelica, A., Trninić-Pjević, A., Mladenović-Segedi, L., Ćetković, N., & Petrović, Đ. (2016). Comparison of the efficiency of clomiphene citrate and letrozole in combination with metformin in moderately obese clomiphene citrate-resistant polycystic ovarian syndrome patients. Srpski arhiv za celokupno lekarstvo, 144(3-4), 146-150.

[17] Bordewijk, E. M., Nahuis, M., Costello, M. F., Van der Veen, F., Tso, L. O., Mol, B. W. J., & van Wely, M. (2017). Metformin during ovulation induction with gonadotrophins followed by timed intercourse or intrauterine insemination for subfertility associated with polycystic ovary syndrome. Cochrane Database of Systematic Reviews, (1).

[18] Cabada-Aguirre, P., López Lopez, A.M., Mendoza, K.C.O. et al. (2023). Mexican traditional medicines for women's reproductive health. Scientific Reports, 13: 2807.

[19] Casteel, C.O. & Singh, G. (2023) Physiology, Gonadotropin-Releasing Hormone. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK558992/

[20] Chrousos, G. P. (2009). Stress and disorders of the stress system. Nature Reviews Endocrinology, 5(7), 374-381. Dickey, R. P., & Holtkamp, D. E. (1996). Development, pharmacology, and clinical experience with clomiphene citrate. Human Reproduction Update, 2(6), 483-506.

[21] Delvigne, A., & Rozenberg, S. (2002). Review of clinical course and treatment of ovarian hyperstimulation syndrome (OHSS). Human Reproduction Update, 8 (5), 559-577.

[22] Devroey, P., Aboulghar, M., Garcia-Velasco, J., & Griesinger, G. (2009). GnRH antagonist: the state of the art. Reproductive BioMedicine Online, 18 (Suppl 2), 1-14.

[23] Dickey, R.P. & Holtkamp, D.E. (1996) Development, Pharmacology and Clinical Experience with Clomiphene Citrate. Human Reproduction Update, 2, 483-506. https://doi.org/10.1093/humupd/2.6.483.

[24] Eini, F., Joharchi, K., Kutenaei, M. A., & Mousavi, P. (2020). Improvement in the epigenetic modification and development competence in PCOS mice oocytes by hydro-alcoholic extract of Nigella sativa during in-vitro maturation: An experimental study. International Journal of Reproductive BioMedicine, 18 (9), 733.

[25] Emokpae, M. A., & Chima, H. N. (2018). Effect of senescence on some apoptosis and oxidative stress markers in infertile normozospermic and oligospermic men: A cross-sectional study. International Journal of Reproductive Biomedicine, 16 (7), 435.

[26] European and Middle East Orgalutran Study Group. (2001). Comparable clinical outcome using the GnRH antagonist ganirelix or a long protocol of the GnRH agonist triptorelin for the prevention of premature LH surges in women undergoing ovarian stimulation. Human Reproduction, 16(4), 644-651.

[27] Fauser, B. C., & Van Heusden, A. M. (1997). Manipulation of human ovarian function: physiological concepts and clinical consequences. Endocrine Reviews, 18 (1), 71-106.

[28] Gabriela Pop, M., Crivii, C., & Opincariu, I. (2018). Anatomy and Function of the Hypothalamus. IntechOpen. doi: 10.5772/intechopen.80728

[29] Gadani, B., Bucci, D., Spinaci, M., Tamanini, C., & Galeati, G. (2017). Resveratrol and Epigallocatechin-3-gallate addition to thawed boar sperm improves in vitro fertilization. Theriogenology, 90, 88-93.

[30] Gerrits, T., & Shaw, M. (2010). Biomedical infertility care in sub-Saharan Africa: a social science-- review of current practices, experiences and viewpoints. Facts, views & vision in ObGyn, 2(3), 194–207.

[31] Gholami, F., Samani, L. N., Kashanian, M., Naseri, M., Hosseini, A. F., & Nejad, S. A. H. (2016). Onset of labor in post-term pregnancy by chamomile. Iranian Red Crescent Medical Journal, 18 (11).

[32] Gurunath, S., Pandian, Z., Anderson, R. A., & Bhattacharya, S. (2011). Defining infertility—a systematic review of prevalence studies. Human reproduction update, 17(5), 575-588.

[33] Hall, J. E, & Hall, M. E. (2020). Guyton and Hall Textbook of Medical Physiology, 14th Edition. ISBN 9780323597128.

[34] Handa, R. J., & Weiser, M. J. (2014). Gonadal steroid hormones and the hypothalamo-pituitary-adrenal axis. Frontiers in Neuroendocrinology, 35(2), 197-220.

[35] Herzog, B. J., Nguyen, H. M. T., Soubra, A., & Hellstrom, W. J. G. (2020). Clomiphene Citrate for Male Hypogonadism and Infertility: An Updated Review. Androgens: Clinical Research and Therapeutics, 62-69. http://doi.org/10.1089/andro.2020.0005

[36] Holland, D., Hatib, K., & Bar-Ya'akov, I. (2009). Pomegranate: botany, horticulture, breeding. Horticultural reviews, 35, 127-191.

[37] Hossein, K. J., Leila, K. J., koukhdan Ebrahim, T., Nazanin, S. J., Farzad, P., & Elham, R. (2015). The effect of pomegranate juice extract on hormonal changes of female Wistar rats caused by polycystic ovarian syndrome. Biomedical and Pharmacology Journal, 8(2), 971-977.

[38] Huijben, M., Lock, T., de Kemp, V., Beck, J., de Kort, L., & van Breda, J. (2022). Clomiphene citrate: A potential alternative for testosterone therapy in hypogonadal males. The Journal of Sexual Medicine, 19 (11, Supplement 4), S22. https://doi.org/10.1016/j.jsxm.2022.08.175.

[39] Huirne, J. A., van Loenen, A. C., Donnez, J., Pirard, C., & D'Hooghe, T. M. (2005). Ovarian hyperstimulation syndrome due to pharmacological ovulation induction: a review. Human Reproduction Update, 11(2), 135-152.

[40] Humaidan, P., Polyzos, N. P., Alsbjerg, B., Erb, K., Mikkelsen, A. L., Elbaek, H. O., ... & Toft, B. G. (2013). GnRHa trigger and individualized luteal phase hCG support according to ovarian response to stimulation: two prospective randomized controlled multi-centre studies in IVF patients. Human Reproduction, 28(9), 2511-2521.

[41] Jaradat, N. & Zaid, A.N. (2019). Herbal remedies used for the treatment of infertility in males and females by traditional healers in the rural areas of the West Bank/Palestine. BMC Complementary and Alternative Medicine, 19, 194 (2019).

[42] Jarow, J.P., Sigman, M., Kolettis, P., Lipshultz, L., McClure, R., Nangia, A., Naughton, C.K., Prins, G.S., Sandlow, J.I. & Schlegel, P.N. (2010). The Optimal Evaluation of the Infertile Male: AUA Best Practice Statement. Available at: https://www.auanet.org/common/pdf/education/clinica l-guidance/Male-Infertility-d.pdf

[43] Jelodar, G. H., & Karami, E. (2013). Effect of hydroalcoholic extract of vitex agnus-castus fruit on ovarian histology in rats with induced Polycystic Ovary Syndrome (PCOS). Journal of BABOL University of Medical Sciences, 15(3), 96-102.

[44] Kamel, R. M. (2013). Management of the infertile couple: an evidence-based protocol. Reproductive Biology and Endocrinology, 11(1), 1-21.

[45] Kesmati, M., Raei, H., & Zadkarami, M. (2007). Effect of Matricaria chamomilla hydroalcolic extract on locomotor activity in the presence and absence of sex gland in male and female adult mice. Shahid Chamran University Journal of Science, 17(1):73-83

[46] Kesmati, M., Raei, H., & Zadkarami, M. (2006). Comparison between sex hormones effects on locomotor activity behavior in presence of matricaria chamomilla hydroalcholic extract in gonadectomized male and female adult mice.

[47] Kettel, L. M., Roseff, S. J., Berga, S. L., Mortola, J. F., & Yen, S. S. (1993). Hypothalamic-pituitary-ovarian response to clomiphene citrate in women with polycystic ovary syndrome. Fertility and sterility, 59(3), 532–538.

[48] Khani, S., Abdollahi, M., Khalaj, A., Heidari, H., & Zohali, S. (2021). The effect of hydroalcoholic extract of Nigella Sativa seed on dehydroepiandrosterone-induced polycystic ovarian syndrome in rats: An experimental study. International Journal of Reproductive BioMedicine, 19(3), 271.

[49] Khodarahmi, S. E., Eidi, A., & Mortazavi, P. (2020). Effect of green tea extract (Camellia sinensis) on levels of sex hormones in letrozole-induced polycystic ovary syndrome (PCOS) in adult female Wistar rats.

[50] Klein, C. E. (2003). The Hypothalamic-Pituitary-Gonadal Axis. In D. W. Kufe, R. E. Pollock, R. R. Weichselbaum, et al. (Eds.), Holland-Frei Cancer Medicine (6th ed.). BC Decker. https://www.ncbi.nlm.nih.gov/books/NBK13386/

[51] Kolibianakis, E. M., Papanikolaou, E., Tournaye, H., Venetis, C. A., Fatemi, H., Tarlatzis, B., & Devroey, P. (2006). Triggering final oocyte maturation using different doses of human chorionic gonadotropin: a randomized pilot study in patients with polycystic ovary syndrome treated with gonadotropin-releasing hormone antagonists and recombinant follicle-stimulating hormone. Fertility and Sterility, 86 (6), 1765-1771.

[52] Lambalk, C. B., Leader, A., Olivennes, F., Fluker, M., & Andersen, A. N. (2006). GnRH agonist for triggering final oocyte maturation in the GnRH antagonist ovarian hyperstimulation protocol: a systematic review and meta-analysis. Human Reproduction Update, 12 (2), 159-168.

[53] Lans, C., Taylor-Swanson, L., & Westfall, R. (2018). Herbal fertility treatments used in North America from colonial times to 1900, and their potential for improving the success rate of assisted reproductive technology. Reproductive biomedicine & society online, 5, 60–81. https://doi.org/10.1016/j.rbms.2018.03.001.

[54] Larsen, U. (2000). Primary and secondary infertility in sub-Saharan Africa. International Journal of Epidemiology, 29 (2), 285–291.

[55] Li, S., Odedina, S., Agwai, I., Ojengbede, O., Huo, D., & Olopade, O. I. (2020). Traditional medicine usage among adult women in Ibadan, Nigeria: a cross-sectional study. BMC complementary medicine and therapies, 20(1), 93. https://doi.org/10.1186/s12906-020-02881-z.

[56] Loutradis, D., Patsoula, E., Minas, V., Koussidis, G. A., Antsaklis, A., & Michalas, S. (2001). The use of gonadotropin-releasing hormone antagonists in the treatment of infertility. Fertility and Sterility, 75 (2), 406-420.

[57] Maeda, K., Ohkura, S., Uenoyama, Y., Wakabayashi, Y., Oka, Y., Tsukamura, H., & Okamura, H. (2010). Neurobiological mechanisms underlying GnRH pulse generation by the hypothalamus. Brain research, 1364, 103 – 115. https://doi.org/10.1016/j.brainres.2010.10.026.

[58] Marques, P., Skorupskaite, K., Rozario, K. S., et al. (2022). Physiology of GnRH and Gonadotropin Secretion. In K. R. Feingold, B. Anawalt, M. R. Blackman, et al. (Eds.), Endotext. MDText.com, Inc. https://www.ncbi.nlm.nih.gov/books/NBK279070/#.

[59] Mbi Feh, M. K., & Wadhwa, R. (2022). Clomiphene. In StatPearls. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK559292/#.

[60] Moenter, S. M., DeFazio, A. R., Pitts, G. R., & Nunemaker, C. S. (2003). Mechanisms underlying episodic gonadotropin-releasing hormone secretion. Frontiers in neuroendocrinology, 24(2), 79–93. https://doi.org/10.1016/s0091-3022(03)00013-x.

[61] Morshedi, M., Khaleghi, M., Azarmi, M., Mohammadzadeh, A., & Gol, A. (2016). The effect of green tea on serum concentrations of estrogen, progesterone and gonadotropins in female rats. Journal of Advances in Medical and Biomedical Research, 24(102), 69-78.

[62] Namwanje, M., & Brown, C. W. (2016). Activins and inhibins: roles in development, physiology, and disease. Cold Spring Harbor perspectives in biology, 8(7), a021881.

[63] Nasimi. D.A.R., Zomorrodi, A., Nazemyieh, H., Fazljou, S. M. B., Sadeghi Bazargani, H., Nejatbakhsh, F., ... & Ahmadi AsrBadr, Y. (2018). Effects of Withania somnifera on reproductive system: a systematic review of the available evidence. BioMed Research International, 2018:4076430. doi: 10.1155/2018/4076430.

[64] Naveen, A., Singh, P., & Chauhan, N.S. (2015). Germination and viability capacity of seeds of Withania somnifera (L.) Dunal. International Journal of Current Science Research, 1(4):67–70.

[65] Nestler, E. J., & Duman, R. S. (2012). Stress, depression, and neuroplasticity: a convergence of mechanisms. Neuropsychopharmacology, 37(1), 137-152.

[66] Okaiyeto, K., & Oguntibeju, O. O. (2021). African Herbal Medicines: Adverse Effects and Cytotoxic Potentials with Different Therapeutic Applications. International Journal of Environmental Research and Public Health, 18(11), 5988.

[67] Ozoemena, O., Ezugworie, J., Mbah, A., Esom, E., Ayogu, B., & Ejezie, F. (2011). Abnormality of pituitary gonadal axis among Nigerian males with infertility: study of patterns and possible etiologic interrelationships. Open access journal of urology, 3, 133–137. https://doi.org/10.2147/OAJU.S22916.

[68] Patwardhan, B., Warude, D., Pushpangadan, P., & Bhatt, N. (2005). Ayurveda and traditional Chinese medicine: A comparative overview. Evidence-Based Complementary and Alternative Medicine, 2(4), 465-473.

[69] Paulson, D. F., & Wacksman, J. (1976). Clomiphene citrate in the management of male infertility. The Journal of Urology, 115 (1), 73-76.

[70] Petrovska B. B. (2012). Historical review of medicinal plants' usage. Pharmacognosy reviews, 6 (11), 1–5. https://doi.org/10.4103/0973-7847.95849.

[71] Polis, C. B., Cox, C. M., Tunçalp, Ö., McLain, A. C., & Thoma, M. E. (2017). Estimating infertility prevalence in low-to-middle-income countries: an application of a current duration approach to Demographic and Health Survey data. Human reproduction (Oxford, England), 32 (5), 1064–1074. https://doi.org/10.1093/humrep/dex025.

[72] Rezk, M., Shaheen, A. E., & Saif El-Nasr, I. (2018). Clomiphene citrate combined with metformin versus letrozole for induction of ovulation in clomiphene-resistant polycystic ovary syndrome: a randomized clinical trial. Gynecological Endocrinology, 34 (4), 298-300.

[73] Richards, J. S., & Pangas, S. A. (2010). The ovary: basic biology and clinical implications. The Journal of clinical investigation, 120 (4), 963-972.

[74] Roychoudhury, S., Agarwal, A., Virk, G., & Cho, C. L. (2017). Potential role of green tea catechins in the management of oxidative stress-associated infertility. Reproductive biomedicine online, 34 (5), 487-498.

[75] Saiyed, A., Jahan, N., Makbul, S. A. A., Ansari, M., Bano, H., & Habib, S. H. (2016). Effect of combination of Withania somnifera Dunal and Tribulus terrestris Linn on letrozole induced polycystic ovarian syndrome in rats. Integrative medicine research, 5(4), 293-300.

[76] Salau, V. F., Erukainure, O. L., Olofinsan, K. A., Omotoso, B. R., & Islam, M. S. (2023). Pomegranate (P. granatum) fruit juice protects against iron-induced oxidative testicular injury via amelioration of oxidative imbalance and modulation of metabolic indices linked to male infertility. Medicine in Omics, 8, 100021. https://doi.org/10.1016/j.meomic.2023.100021.

[77] Sapolsky, R. M. (2015). Stress and the brain: Individual variability and the inverted-U. Nature Neuroscience, 18(10), 1344-1346.

[78] Sawant, S., & Bhide, P. (2019). Fertility treatment options for women with polycystic ovary syndrome. Clinical Medicine Insights: Reproductive Health, 13, 1179558119890867.

[79] Sharpe-Timms, K. L. (1997). Gonadotropin-releasing hormone and its receptor in the human ovary. Biology of Reproduction, 57 (2), 359-366.

[80] Sharpe, A., Morley, L. C., Tang, T., Norman, R. J., Balen, A. H., & Cochrane Gynaecology and Fertility Group. (1996). Metformin for ovulation induction (excluding gonadotrophins) in women with polycystic ovary syndrome. Cochrane Database of Systematic Reviews, 2019 (12).

[81] Shoorei, H., Khaki, A., Ainehchi, N., Taheri, M. M. H., Tahmasebi, M., Seyedghiasi, G., ... & Raza, S. H. A. (2018). Effects of Matricaria chamomilla extract on growth and maturation of isolated mouse ovarian follicles in a three-dimensional culture system. Chinese Medical Journal, 131(02), 218-225.

[82] Shpakov A. O. (2021). Improvement Effect of Metformin on Female and Male Reproduction in Endocrine Pathologies and Its Mechanisms. Pharmaceuticals (Basel, Switzerland), 14 (1), 42. https://doi.org/10.3390/ph14010042.

[83] Silva, F. V., Dias, F., Costa, G., & Campos, M. D. G. (2018). Chamomile reveals to be a potent galactogogue: the unexpected effect. The Journal of Maternal-Fetal & Neonatal Medicine, 31(1), 116-118.

[84] Smith, S. M. VW (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues in clinical neuroscience, 383-95.

[85] Sönmezer, M., Türkçüoğlu, I., & Atabekoğlu, C. S. (2008). Triggering with human chorionic gonadotropin or a gonadotropin-releasing hormone agonist in gonadotropin-releasing hormone antagonist-treated oocyte donor cycles: findings of a large retrospective cohort study. Fertility and Sterility, 90 (1), 231-233.

[86] Speroff, L., Fritz, M. A., & Authors, Various. (2012). Clinical Gynecologic Endocrinology and Infertility. Lippincott Williams & Wilkins.

[87] Stephens, M. A. C., & Wand, G. (2012). Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol research: current reviews, 34(4), 468.

[88] Subair, B. K. & Ade-Ademilua, O. E. (2022). Traditional Treatment of Female Infertility: Yoruba Perspective. Nigerian Journal of Botany, 35(1): 47-58.

[89] The Goserelin Study Group. (1984). Goserelin acetate in endometriosis: a randomised comparison with danazol. British Journal of Obstetrics and Gynaecology, 91(7), 678-688.

[90] Thomson, A. B., & Kalra, S. K. (2008). Ovulation induction in perspective. Clinical Medicine & Research, 6 (1), 22-32.

[91] Tulandi, T., & Martin, J. (2013). Potential risk of ovarian cancer associated with the use of ovulation-stimulating drugs for infertility treatment. The Journal of Obstetrics and Gynaecology Research, 39 (12), 1735-1740.

[92] Van Poppel, H., Tombal, B., & de la Rosette, J. J. (2017). Degarelix: a novel gonadotropin-releasing hormone (GnRH) receptor blocker--results from a 1-year, multicentre, randomised, phase 2 dosage-finding study in the treatment of prostate cancer. European Urology, 54 (4), 805-813.

[93] Whirledge, S., & Cidlowski, J. A. (2017). Glucocorticoids and reproduction: traffic control on the road to reproduction. Trends in Endocrinology & Metabolism, 28(6), 399-415.

[94] Witchel, S. F., Oberfield, S. E., & Pena, A. S. (2019). Polycystic ovary syndrome: pathophysiology, presentation, and treatment with emphasis on adolescent girls. Journal of the Endocrine Society, 3(8), 1545-1573.

[95] World Health Organisation (2023). Global Prevalence of Infertility. https://www.who.int/news/item/04-04-2023-1-in-6-people-globally-affected-by-infertility#:~:text=Large%20numbers%20of%20people%20are,report%20published%20today%20by%20WHO.

[96] Wu, Y., Tu, M., Huang, Y., Liu, Y., & Zhang, D. (2020). Association of Metformin with Pregnancy Outcomes in Women With Polycystic Ovarian Syndrome Undergoing In Vitro Fertilization: A Systematic Review and Meta-analysis. JAMA Network Open, 3(8), e2011995. doi:10.1001/jamanetworkopen.2020.11995.

[97] Xu, Q., Bauer, R., Hendry, B. M., Fan, T. P., Zhao, Z., & Duez, P. (2013). The quest for modernisation of traditional Chinese medicine. BMC Complementary and Alternative Medicine, 13(1), 132.

[98] Yakubu, M. T., & Akanji, M. A. (2011). Effect of aqueous extract of Massularia acuminata stem on sexual behaviour of male Wistar rats. Evidence-Based Complementary and Alternative Medicine, 2011.

[99] Ye, H., & Shaw, I. C. (2020). Dietary isoflavone-induced, estrogen receptor-β-mediated proliferation of Caco-2 cells is modulated by gallic acid. Food and Chemical Toxicology, 145, 111743.

[100] Youssef, M. A., Van der Veen, F., Al-Inany, H. G., Griesinger, G., Mochtar, M. H., Aboulfoutouh, I., ... & van Wely, M. (2010). Gonadotropin-releasing hormone agonist versus HCG for oocyte triggering in antagonist-assisted reproductive technology. Cochrane Database of Systematic Reviews, (1), CD008046.

[101] Yu, Y., Fang, L., Zhang, R., He, J., Xiong, Y., Guo, X., ... & Sun, Y. (2017). Comparative effectiveness of 9 ovulation-induction therapies in patients with clomiphene citrate-resistant polycystic ovary syndrome: a network meta-analysis. Scientific reports, 7(1), 3812.

[102] Zanchi, M. M., Manfredini, V., dos Santos Brum, D., Vargas, L. M., Spiazzi, C. C., Soares, M. B., ... & Santos, F. W. (2015). Green tea infusion improves cyclophosphamide-induced damage on male mice reproductive system. Toxicology reports, 2, 252-260.