Comparative Analysis of the Biochemical Mechanism of Hormonal and Non-Hormonal Contraceptives

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Abstract:

Hormonal and nonhormonal contraceptives are used in a diversity of methods across the globe to provide treatment and benefits to women of varying needs. Contraceptives affect biochemical pathways that regulate reproduction and menstruation[5], leading to a wide range of effects that differ between individuals. Health care professionals give insight to prescribe the best fitting contraceptive for each patient, however there is not enough accessible information for women to understand how each method affects their bodies and for them to advocate for which method suits their health and lifestyle needs. This article directly compares the biochemical pathways of hormonal and nonhormonal contraceptives to provide accessible information to better decide which method they prefer through evaluation of the direct and indirect effects of each contraceptive. By comparing the structure and metabolic aspects of exogenous and endogenous steroid hormones, how hormonal contraceptives affect the Hypothalamus-Pituitary-Gonadal (HPG) axis, and how nonhormonal contraceptives induce a cytotoxic inflammatory pathway, readers can understand why their symptoms arise and how pregnancy is prevented. This article displays the effects of birth control and risks as well as how specific menstrual cycle symptoms can change while using varying methods.

Introduction:

Contraceptives are widely used in women of ages 15-44 with a large variety of reasons from prevention of pregnancy to treatment of disease and enhancement of reproductive health[5]. Hormonal and nonhormonal contraceptives are available for use with a variety of methods to which a patient may achieve contraception. Although the mechanisms of contraceptives vary, each relies on the menstrual cycle to act through either systematic endocrine or local uterine effects. Hormonal contraceptives deliver exogenous analogs of steroid hormones through pills, injections, implants, vaginal rings, and intrauterine devices to suppress the Hypothalamus-Pituitary-Gonadal (HPG) axis and regular menstrual actions which lead to ovulation and pregnancy[1,5]. On the other hand, nonhormonal birth control methods rather use copper intrauterine devices or spermicides and physical blockades to achieve contraception through local inflammatory and other physiological effects[5,18].

Although there is much information regarding the different types of contraceptives, there is a lack of sustainable comparison of their mechanisms at the biochemical level. This article aims to provide an evidence-based explanation for patients who wish to begin contraceptive use to make an educated decision on which method to use. Each contraceptive method presents side effects and precautions that can be unfavorable or tolerable depending on each patient and their individual health needs such as menstrual regulation, acne management, or high-risk factors[5,11].

This paper examines the influence of structural modifications in ethinyl estradiol and progestins across the HPG axis and local uterine mechanisms in hormonal contraceptives. These exogenous steroid hormones have been synthesized to obtain more effective molecules in metabolism, receptor binding, and pharmacokinetics to suppress hormone fluctuation associated with ovulation and sperm implantation which mediate pregnancy[10, 11, 31, 32, 35]. Along with this, nonhormonal mechanisms such as a cytotoxic inflammatory reaction and local uterine changes that provide an unstable environment for reproduction processes are reviewed to compare the contraceptive pathways and their varying biochemical and physiological effects[18]. Understanding how birth control mechanisms act at the biochemical level allows the prediction of physiological effects and the management of side effects and disease.

Endogenous vs Exogenous Steroid Hormones:

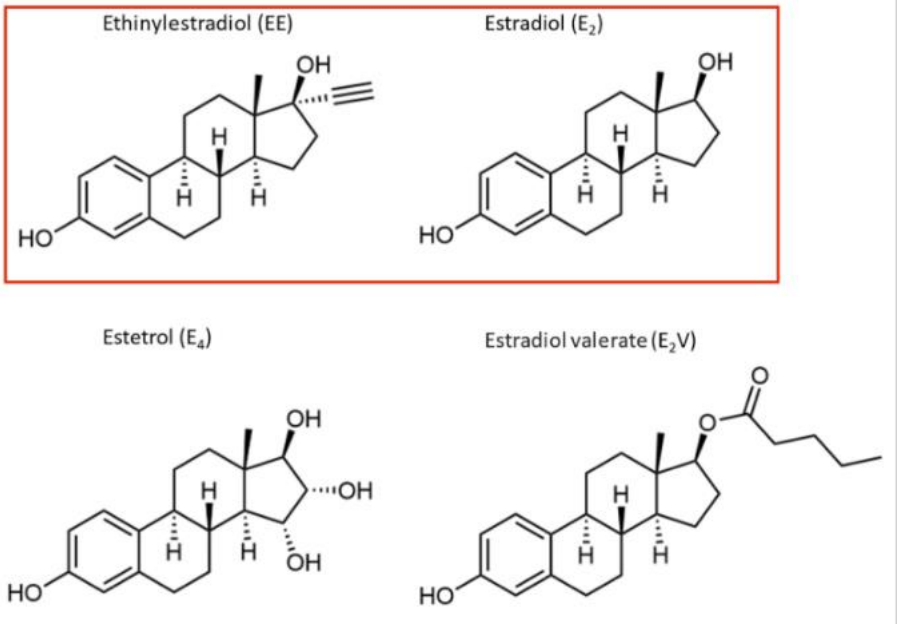

Figure 1 - Structural diagram of estrogenic components used in hormonal birth control. The most prominent components are contained in the red box (EE and E2). The figure shows the structural differences in the natural estrogen (Estradiol E2) and synthetic estrogen (Ethinyl estradiol EE) referenced throughout this paper. The molecules have identical steroid backgrounds apart from the differing functional groups at C17. EE has a hydroxyl and an ethinyl group, whereas E2 only has a hydroxyl group. Adapted from reference 32.

Hormonal contraceptives contain synthetic progestogenic components as well as, in some formulations, estrogenic components. The exogenous steroid hormones are designed to mimic or modify the effects of the HPG axis to achieve contraception. The estrogenic component used in hormone contraceptives is ethinyl estradiol (EE), which,

seen from Figure 1, is structurally identical to the endogenous estradiol (E2), apart from a single modification at carbon 17. Estradiol is a four-ring structure that has two hydroxyl groups on carbons 3 and 17. Ethinyl estradiol differs from the natural hormone by its ethinyl group which accompanies its hydroxyl at carbon 17[32]. Figure 1 shows the structural difference that makes the synthetic estrogen component suitable for the prevention of ovulation. The endogenous estrogen has a higher affinity for the α and β isoforms of the estrogen receptor (ER), however, the additional functional group of the exogenous estrogen grants it prolonged receptor interactions through increased receptor affinity and stability, as well as a decreased metabolic breakdown[32]. The structural changes at carbon 17 drastically affect the bioavailability and half-life of EE, allowing it to outcompete endogenous estrogen at the ER. Estradiol's hydroxyl groups are susceptible to liver enzymes for oxidation and conjugation which reduce the molecule to its water-soluble precursor, estrone[32]. Because of this, naturally produced estrogen molecules can quickly be inactivated and cleared from the body. The ethinyl group at carbon 17 on EE sterically hinders its hydroxyl group to prevent conjugation and oxidation, allowing the molecule to survive hepatic first pass metabolism and continuously activate and bind tightly to receptors on the HPG axis[32]. This small structural difference allows the synthetic estrogen to follow the same biochemical pathway as the natural estrogen, while exerting stronger and more sustained physiological effects due to its longer half-life and higher potency.

Table 1 – Delivery Methods and Their Associated Progestins

Delivery Method	Progestin Used	Generation
Combined Oral Contraceptive (COC)	Norgestimate, Drospirenone	3rd, 4th
Progestin Only Pill (POP)	Norethindrone, Drosprienone	1st, 4th
Injection	Medroxyprogesterone Acetate	N/A
Subdermal Implant	Etonogestrel	3rd
Hormonal IUD	Levonorgestrel	2nd
Vaginal Ring	Etonogestrel	3rd

Figure 2 – This table provides an organized display of each hormonal birth control mentioned in this paper, along with the progestin it contains. The generation of each progestin is also listed to show development timeline and receptor selectivity. The first and second generations generally have more androgenic activity, whereas the third and fourth generations have improved receptor selectivity and tolerability. Adapted from references 10, 11, 31, and 35.

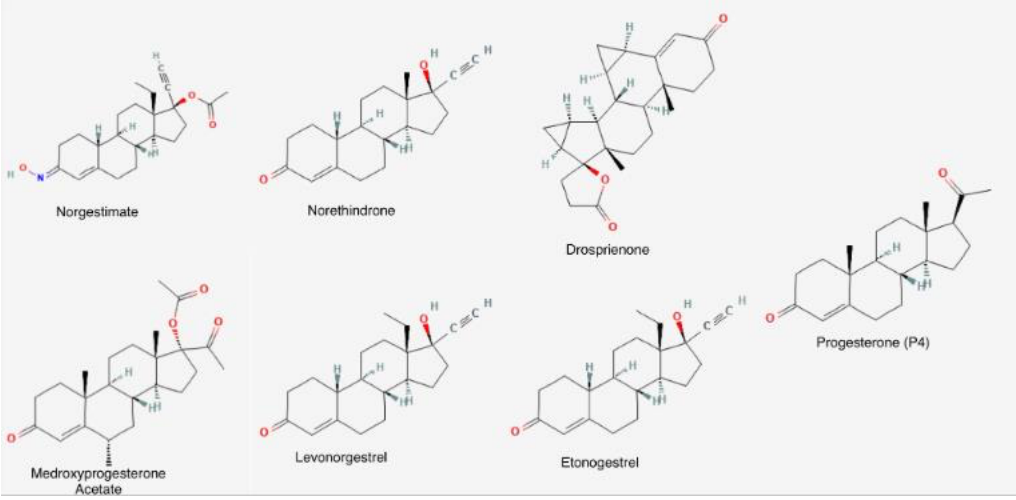

Figure 3 – Structural diagram of progestogenic components used in hormonal birth control and demonstrates how they differ from endogenous progesterone. Norgestimate lacks the C19 methyl, has an ethyl group rather than a methyl at C13, and has an ethinyl group at C17. Norethindrone lacks the methyl group at C19 and the addition of an ethinyl at C17. Drospirenone is not a derivative of progesterone, as it mimics spironolactone with its lactone ring. Medroxyprogesterone acetate has a methyl group at C6 and an acetate ester at C17. Levonorgestrel lacks the C19 methyl group, has an ethyl group instead of a methyl at C13, and has an ethinyl group at C17. Etonogestrel is a more refined version of levonorgestrel. Adapted from references 22, 23, 24, 25, 26, and 27.

Modifications to estrogen enhance the pharmacokinetics of the molecules, while progestins further diversify the receptor interactions and are the primary components of hormonal contraceptives. Progestins are synthetic analogs of endogenous progesterone (P4) that, like estradiol, are designed to mimic the natural hormones effect along the HPG

axis to achieve contraception while altering bioavailability, half-life, and receptor binding properties. The endogenous hormone is rapidly metabolized in the body compared to the exogenous hormones due to its ketone group at carbon 20 and its hydroxyl group at carbon 17, making it susceptible to oxidation and conjugation into water-soluble metabolites[29]. This gives P4 a low bioavailability that clears the endogenous hormone in first-pass metabolism. There are various structural modifications in progestins that alter the metabolic activity, receptor selectivity, and bioavailability of the hormones, which can be seen in Figure 3. The removal of the methyl group on progesterone's carbon 19 increases the molecules activity at the progesterone receptor (PR) [31]. This applies to norethindrone, levonorgestrel, etonogestrel, and norgestimate allowing them to prolong their receptor activity. The addition of either an ethinyl or acetate to carbon 17 on norethindrone, levonorgestrel, etonogestrel, and medroxyprogesterone acetate allows the progestins to block oxidation and conjugation through steric hinderance[31]. Drospirenone, as it is not a progesterone derivative, contains a lactone ring that increases the metabolic stability of the molecule[31]. The progestin is structurally similar to P4, allowing it to bind to the receptor. All progestins used in hormonal contraceptives have a longer half-life than endogenous progesterone, allowing them to exert their effects longer and prevent fluctuations of natural hormones required for ovulation.

How Hormonal Contraceptives Affect the Biochemical and Physiological Pathways:

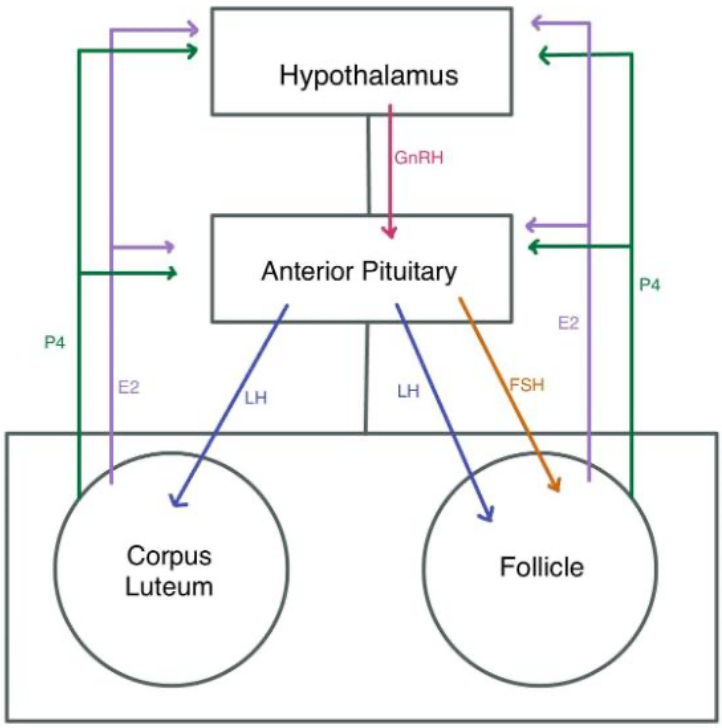

Figure 4 – Systematic diagram of the HPG axis. Starting at the hypothalamus GnRH movement is depicted by a pink arrow to the anterior pituitary. From the pituitary blue arrows for LH point to the corpus luteum and follicle, and a blue arrow for FSH points to the follicle to show the gonadotrophins signaling targets. Green arrows for progesterone and purple arrows for estrogen point to the hypothalamus and anterior pituitary to demonstrate the positive and negative feedback loops in the HPG axis. Adapted from reference 20.

There are numerous birth control methods that contain synthetic hormones which alter biochemical pathways or local physiological responses to achieve contraception. Progesterone only pills (POP), combined oral contraceptives (COC), injections, vaginal

rings, patches, and subdermal implants exert their effects through the suppression of usual Hypothalamus-Pituitary-Gonadal (HPG) axis activity with minor local effects of the reproductive system[5], as seen in Figure 4. The hormonal intrauterine device (IUD) has the opposite effect primarily acting locally with slight suppression of the HPG axis[5].

The HPG axis begins in specialized GnRH neurons located in the hypothalamus that synthesize the gonadotrophin releasing hormone (GnRH). GnRH s a hypothalamic decapeptide that controls the downstream mechanisms of steroid hormone production[18]. The axon terminals release GnRH in intermittent pulses of which fluctuate throughout the stages of the menstrual cycle. The GnRH travels through the hypothalamo-hypophyseal blood vessel portal to the capillary bed of the anterior pituitary, where it binds to its receptor, GnRHR[18]. The Type I mammalian gonadotrophin releasing hormone receptor (GnRHR) is a 7-transmembrane G coupled protein receptor which lacks a cytoplasmic carboxyl-terminal tail, preventing GPCR kinase phosphorylation, β-aresstin signaling inhibition, and dynamin associated endocytosis of the receptor[18]. This allows the desensitization and internalization of the receptor to carry out slower, facilitating the protein signal duration of the GnRH pulse. The binding of GnRH to its receptor induces the release of glycoprotein dimers, the follicle stimulating hormone (FSH) and luteinizing hormone (LH) necessary for reproduction. FSH and LH share a common α subunit but have unique β subunits which are encoded for by the GnRH pulse frequency through an unknown process[18]. It is believed that the GnRHR binding induces G coupled proteins that stimulate phospholipase C, leading to production of second messengers that increase intracellular Ca2+ to activate MAPK and PKC pathways[21]. This ultimately promotes

hormone secretion while regulating the transcription of βFSH and βLH to control the synthesis and release of the gonadotrophins[18].

As the gonadotrophins circulate through the blood stream to the ovaries, they bind to their respective receptors on specialized cells around the follicle to synthesize estrogen and progesterone in a two-cell two-gonadotrophin process[8]. The thecal cells make up the outer follicular later, while the granulosa cells form the inner layer surrounding the oocyte. In the early follicular phase, FSH binds its receptors on granulosa cells to stimulate the expression of aromatase, an enzyme that functions to convert androgens within the cell to estrone, which is then converted to estradiol by 17 β-HSD-1[8]. In the late follicular phase, LH binds to its receptors on thecal cells. Within these cells, LH stimulates the production of a precursor to estrogen, androstenedione, which is diffused from thecal cells to granulosa cells for the synthesis of estradiol[12]. This estradiol is used to grow oocyte containing follicles as well as to thicken the uterine lining in preparation for implantation. In the luteal phase, granulosa cells acquire LH receptors through luteinization[12]. This process occurs after ovulation due to enzyme shifting and the continuation of meiosis in the oocyte after an increase in LH[12]. During luteinization the follicle membrane breaks, allowing granulosa cells to form the corpus luteum where the P450 cleavage enzyme converts cholesterol to pregnenolone[12]. 3 β-hydroxysteroid dehydrogenase then converts the pregnenolone to progesterone which is used to prepare the uterine lining for implantation of the fertilized egg[12].

This biochemical mechanism is dependent on endogenous estrogen and progesterone to regulate follicle growth and ovulation through feedback loops represented

by the arrows labeled E2 and P4 in Figure 4. Throughout the follicular phase, the system rises from a weak to strong negative feedback loop until the formation of a dominant follicle[15]. Progesterone, the dominant suppressor, reduces GnRH responsiveness to suppress the synthesis of LH and prevent the growth of a second follicle[15]. Inhibin B prominent in this phase suppresses FSH expression[15], while estradiol drives follicle development and maintains steady upstream hormone levels. Right before ovulation, estradiol levels spike, causing a positive feedback window where the binding of E2 to the ER in the hypothalamus causes an increased GnRH pulse and LH production[20]. With inhibin B suppressing FSH, estradiol reaches its threshold to send an LH surge to the ovaries, releasing the oocyte and beginning ovulation[15]. The feedback becomes negative again as E2 levels subside, and the corpus luteum produces progesterone and inhibin A to prevent a second ovulation and premature follicle development[15].

Most hormonal contraceptives exploit the tightly regulated HPG axis to prevent ovulation and suppress the actions of the mechanism. Hormonal birth control contains solely a progestin or is a combination of a progestin and ethinyl estradiol. Progestin only contraceptives (POPs, injections, implants, and the IUD) and combined contraceptives (COCs, vaginal rings, and patches) suppress the hormones in the upstream HPG axis through competitive binding of exogenous and endogenous steroid hormones. Progestin is the main suppressor of FSH and LH and has secondary effects to prevent pregnancy through thickening cervical mucus to reduce sperm mobility, thinning endometrial lining to prevent implantation, and slowing egg movement through the fallopian tube[5]. These local effects are the primary result of a hormonal IUD, as it has minimal HPG axis suppression.

By administering a controlled dose of progestin or combined contraceptives, the exogenous hormones keep the HPG axis in a negative feedback loop by mimicking the endogenous steroid hormones. The moderate level of progestin maintains a low expressivity of LH to prevent ovulation through blocking the LH surge and reduces circulating FSH to prevent viable follicle development[30]. The progestin also reduces GnRH responsivity, preventing downstream hormone fluctuation. Ethinyl estradiol is administered in a low dose to prevent the rising estrogen levels that trigger the LH surge, slightly aiding in the dominant suppressor maintaining a negative feedback loop[15]. A mathematical model study was conducted to analyze dosages of COCs and POPs to predict which prescriptions would reach a total contraception, represented by the flattened line on the LH graph[33]. A black "X" was noted at the peak of each LH diagram to show the threshold which triggers ovulation. From Figure 5, the data collected from literature was plotted on the concentrations of estrogen, progesterone, LH, and FSH in a normal menstrual cycle to compare to Figures 6, 7, and 8. Figure 6 shows a lose dose of progestin reaching a biological contraceptive state, as the estrogen and LH levels did not have a spike to trigger ovulation. However, cycle-like oscillations were observed that can cater to biological functions associated with viable fertilization. A higher dose of progestin in Figure 7 and a combined dose of progestin and ethinyl estradiol in Figure 8 proved a more reliable, total contraceptive state[33]. Total contraception is preferred as no fluctuations in HPG axis hormones completely restrains ovulation[33]. This model did not account for inhibin A in the luteal phase, only inhibin B in the follicular phase, resulting in elevated FSH levels that do not accurately represent the contraceptive effects[33].

Regardless, this model demonstrates pregnancy prevention through consistent administration of exogenous steroid hormones.

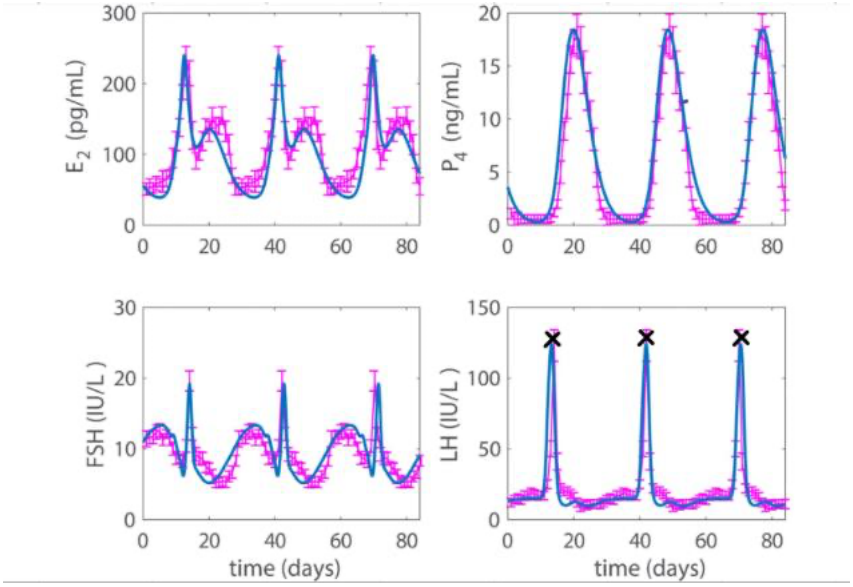

Figure 5 – Diagram provides a 3-cycle model output of the normal menstruation cycle for estrogen, progesterone, FSH, and LH. The magenta data points show the experimental data collected from literature used to compare against the blue solid line of the data from the study. The black X in the graph of the luteinizing hormone marks the peak of the LH surge that triggers ovulation. This model was assumed to run long enough to settle in a steady state to show long term behavior with and without contraceptive dosages. Adapted from reference 33.

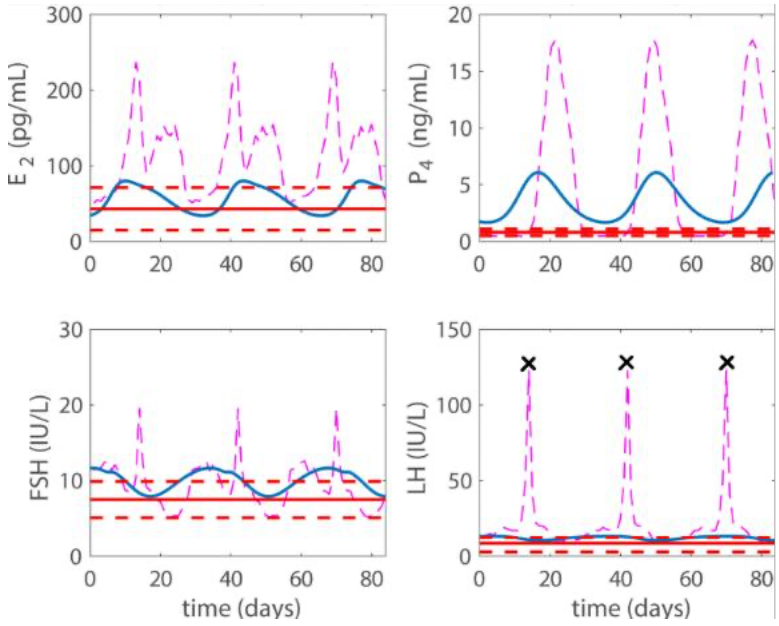

Figure 6 – Diagram shows the same 3-cycle model output for a low dose (0.6 ng/mL) of progestin for estrogen, progesterone, FSH, and LH. The magenta data points show the experimental data collected from literature used to compare against the blue solid line of the data from the study. The red solid line shows the mean max, and the red dotted line shows the standard deviation of expected outcome of the contraceptive. The black X in the graph of the luteinizing hormone marks the peak of the LH surge that triggers ovulation. This model shows a biological contraceptive state reached. Adapted from reference 33.

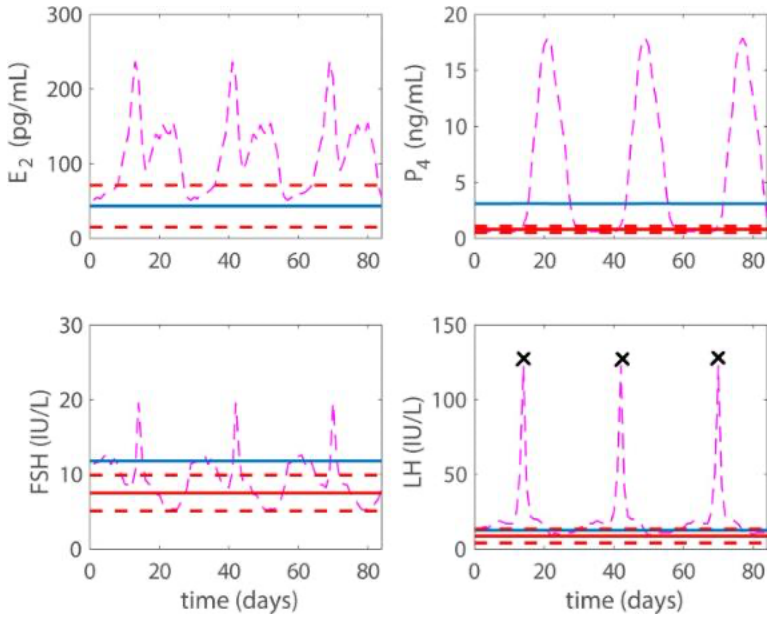

Figure 7 – Diagram shows the same 3-cycle model output for a high dose (1.3 ng/mL) of progestin for estrogen, progesterone, FSH, and LH. The magenta data points show the experimental data collected from literature used to compare against the blue solid line of the data from the study. The red solid line shows the mean max, and the red dotted line shows the standard deviation of expected outcome of the contraceptive. The black X in the graph of the luteinizing hormone marks the peak of the LH surge that triggers ovulation. This model shows a total contraception state reached. Adapted from reference 33.

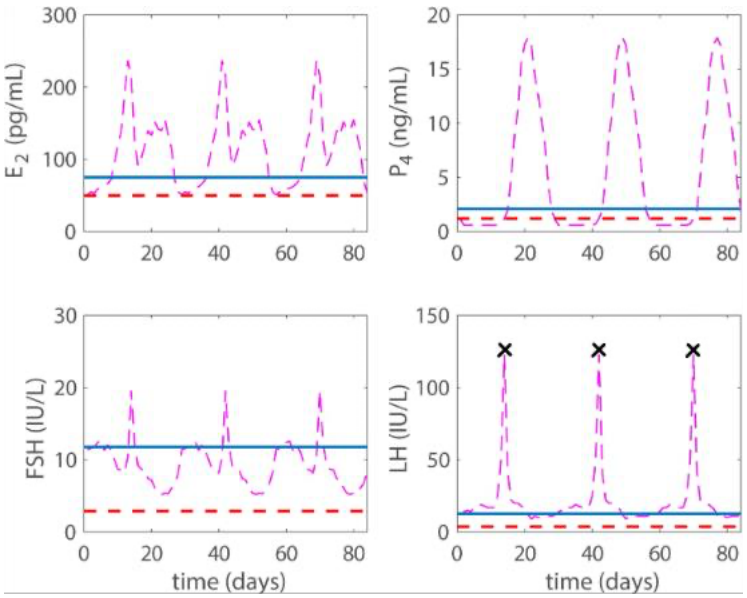

Figure 8 – Diagram shows the same 3-cycle model output for a combined dose of progestin (0.6 ng/mL) and ethinyl estradiol (40 pg/mL) of progestin for estrogen, progesterone, FSH, and LH. The magenta data points show the experimental data collected from literature used to compare against the blue solid line of the data from the study. The red solid line shows the mean max, and the red dotted line shows the standard deviation of expected outcome of the contraceptive. The black X in the graph of the luteinizing hormone marks the peak of the LH surge that triggers ovulation. This model shows a total contraception state reached. Adapted from reference 33.

Symptoms of Hormonal Contraceptives:

Some side effects of hormonal contraceptives are more severe in patients with underlying conditions or unhealthy lifestyle habits, however for an individual with normal health, side effects depend on the contraceptive method. Irregular or heavier bleeding is most observed in progestin only methods such as the POP, hormonal IUD, and subdermal implant due to the endometrium thinning[5]. Associated progestins are levonorgestrel, etonogestrel, and norethindrone. This effect is less common in combined contraceptives as ethinyl estradiol aids in the stabilization of the lining[5]. Amenorrhea, or the lack of a menstruation, is commonly associated with high dosages and long exposure of levonorgestrel, etonogestrel, and medroxyprogesterone acetate in the hormonal IUD, implant, and injections[5]. Due to the long lasting, strong suppression in these methods the endometrium does not build enough lining to shed it for menstruation. Androgenic effects such as acne are due to the higher receptor activity of progestins being able to bind to androgen receptors[31]. This side effect is seen in contraceptives containing levonorgestrel and norethindrone in the IUD, some COCs, and POPs. Some COCs, however, use drospirenone, or other third generation progestins shown in Figure 2, which have lower androgen receptor activity and lower acne when in use. Weight gain is most observed in high-dose, long-acting contraceptives such as the injection due to prolonged systemic exposure to medroxyprogesterone acetate, which can influence appetite regulation and fluid retention[5]. This effect is less pronounced in other progestin-only methods, as their dosages and sustained activity are lower. Combined contraceptives are associated with minimal weight gain, as the low progestin dose and presence of ethinyl estradiol stabilize

fluid balance and limit significant metabolic effects[5]. For a normally healthy individual, all side effects and delivery methods should be considered to determine which contraceptive fits their needs most.

Nonhormonal Contraceptive Mechanism:

In contrast to hormonal contraceptives, nonhormonal contraceptives function independently of the HPG axis and rather use local physical and chemical mechanisms that do not alter endogenous hormone signaling. The most prominent nonhormonal contraceptive is the copper IUD which uses a cytotoxic inflammatory reaction to prevent sperm cells from fertilizing an egg[19]. The copper metal on the plastic frame is inserted into the uterus where the copper atoms undergo a controlled oxidation[34]. Electrolytes facilitate charge transfer in the uterine fluid, enabling electron flow from the surface of the copper in an oxidation reaction[34]. This oxidation is coupled by the reduction of dissolved oxygen which accepts the electrons, then subsequently binds to the available H+ ions in the uterine fluid to form water molecules. The copper on the surface of the device is not highly reactive, forming a tight oxide layer which slows further oxidation without completely halting the ion release. This provides a long lasting and persistent process that allows the device to remain effective for 5-10 years[34].

The positively charged copper ions released from the device disrupt sperm function by inducing membrane damage and altering cellular ion balance. At high concentrations,

copper can cause displacement of other ions associated with cell membranes, destabilizing the bilayer. Because of this, copper ions can disrupt the permeability of cell membranes, ultimately compromising the internal environment or causing apoptosis[29]. Some copper ions may enter the sperm cell and bind to mitochondrial enzymes in the electron transport chain, reducing electron flow and lowering ATP production[29]. With low ATP production, the sperm have less energy to power the dynamin motor proteins in the flagellum, causing less efficient movement through the cervical mucus to the oocyte for fertilization. With lower mobility of sperm cells, they may not engage in the necessary enzyme mediated release for sperm to penetrate the egg called the acrosome reaction, reinforcing the copper IUD's contraceptive effect[13, 18, 19, 34].

Spermicides use a similar process to disrupt sperm membranes and reduce motility. The nonionic surfactant nonoxyl-9 increases the permeability of the sperm cell membranes by inserting themselves into the lipid bilayer[5]. This causes ions and small molecules to enter the cell, leading to membrane damage which ultimately immobilizes and kills the cells. Spermicides are not commonly used as they must be inserted into the vagina prior to intercourse[5]. Other contraceptives such as cervical caps or condoms used strictly depend on physically blocking the sperm from entering the cervix.

Symptoms of Nonhormonal Contraceptives:

Spermicides and the copper IUD may elicit side effects and symptoms. The copper IUD can cause heavier, longer, or irregular periods, especially the months following

insertion[5]. The local inflammatory reaction can increase contractility and endometrial irritation, causing shedding and elevated cramping or pelvic pain. The copper IUD may severely increase the risk of an ectopic pregnancy, where the fertilized egg implants outside of the uterus[5]. Spermicides themselves are not contraceptionally efficient, and can cause vaginal irritation, urinary tract infections, or discomfort[5]. This is caused by the disruption of epithelial membranes of the vagina and cervix. Because of this, apart from condoms, the copper IUD is favored but may cause severe side effects, especially in individuals with heavy or irregular menstruation.

Conclusion:

The biochemical mechanisms of hormonal and nonhormonal contraceptives provide fundamentally distinct methods for preventing a viable pregnancy. Hormonal contraceptives function through the suppression of the HPG axis by use of structurally modified steroid hormones which enhance receptor binding, metabolic stability, and half-life. These contraceptives mimic the natural systemic mechanism to sustain a constant negative feedback loop, preventing necessary processes that lead to ovulation and pregnancy. Nonhormonal contraceptives act through a physical block of sperm cells from fertilization, a cytotoxic inflammatory reaction, or local uterine environmental changes to prevent viable fertilization. This paper provides a comparative analysis of the contraceptive mechanisms and side effects to supply patients with a means to determine which method

is most suitable for them. Patients with heavy or painful menstruation benefit from combined oral contraceptives such as COCs, vaginal rings, and patches, and experience an increased severity in symptoms when using progestin only contraceptives or intrauterine devices[5]. Patients opposed to weight fluctuations should avoid contraceptives with a high, long-lasting dose and rather use a contraceptive with a more frequent administration[5]. Acne prone patients benefit from contraceptives containing a third-generation progestin like drospirenone and avoid later generations which have higher androgenic effects[31]. For an individual with a normal menstruation, a combined oral contraceptive with noregestimate or the copper IUD may be the most fitting contraceptive. The later generation progestins in COC accompanied with ethinyl estradiol closely mimics the HPG axis and provides a regular menstruation with minimal symptoms, whereas the copper IUD does not affect the individual hormonally and does not require a daily regimen.

The most suitable method of contraception not only depends on the underlying conditions and symptom preference of the individual, but also on the most suitable delivery method. Contraceptives are most effective when used without deviance from instructed delivery. Because of this, many individuals benefit from using implants, rings, IUD's, or injections to avoid a missed dose. To some, these methods may be too invasive or painful, leaving some individuals to prefer oral contraceptives. This leaves a contraceptive method to be personal and depend on the individual.

There is still much about contraceptive mechanisms that remains unknown, such as the synthesis of βFSH and βLH from GnRH pulse frequencies. Further research on aspects not fully understood can give rise to more contraceptive methods to become

available that fit a broader range of induvial needs. Furthermore, research to find contraceptives catered to males would diversify options to prevent pregnancy. Despite this, there is a variety of contraceptives for women to choose from. This review highlights how an evidence-based understanding can provide guidance in selecting the contraceptive method that best balances safety and individual health needs for interested women.

AI tools were not used to generate scientific content. All scientific content, analysis, and conclusions were reviewed and revised by the author

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