Biochemical Mechanisms of Contraceptive Action: Levonorgestrel-Releasing Hormonal Intrauterine Devices v. Copper-Based Intrauterine Devices

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Abstract

The development of intrauterine devices nearly 70 years ago provided menstruating individuals with an extremely appealing contraceptive option that is long-term, highly-effective, and reversible. However, research into the biochemical basis behind how these systems elicit their contraceptive action has plateaued since entering the 21st century, with the pain experienced upon insertion and a host of other adverse effects that accompany intrauterine device use becoming main topics of discussion amongst the medical community and beyond. This review focuses on compiling previous research into the mechanism of action of both hormonal and copper-based intrauterine devices to provide insight into how these devices invoke contraceptive action at a biochemical level, while also highlighting the immense need for more contemporary research. Currently, there are a number of promising physiological processes hypothesized to be the target of biochemical contraceptive action. Further research into these physiological targets will undoubtedly contribute to improving these vital devices and limiting the multitude of adverse effects impacting the everyday life of users.

Introduction

Contraception refers to the use of various medications, devices, and practices to deliberately prevent pregnancy. Documentation of contraceptive use among humans dates as far back as 2000 B.C. with the Ancient Egyptians using everything from herbs to amulets to prevent pregnancy [1]. The contraceptive methods of the modern age, more commonly referred to as birth control, have evolved far past these primitive endeavors. Contemporary practices range from single-use methods like condoms to irreversible sterilization via tubal ligation. However, many individuals are interested in birth control options that find a happy medium between those two. They seek a method that is highly effective, long-lasting, and most importantly, reversible. Intrauterine devices are that happy medium.

While these devices have undoubtedly gained immense popularity over the last 30 years, they have also been the subject of scrutiny due to certain adverse effects. The scope of understanding of the biochemical mechanism through which these devices—both hormone releasing and copper releasing—exert their contraceptive and adverse effects is still rather limited. This paper will provide insight into the typical processes involved in human reproduction, the general role of contraceptives in working to impede these processes, the mechanisms of action of both hormonal and copper-based intrauterine devices, and the advantages and disadvantages of each method. These insights culminate to achieve the principal goal of this review, compiling the current research into the biochemical mechanism of action of both hormonal and copper-based intrauterine systems while simultaneously highlighting the adverse effects which constitute the ever-present need for continued research.

Background: Reproduction and Contraceptives

The process of embryogenesis in human beings is a complicated and highly regulated multi-step pathway. Beginning with fertilization and ending with organogenesis, there are endless opportunities for error and failure of the process. Contraceptives, devices and drugs designed to prevent pregnancy, function primarily to interfere with a variety of steps during and leading up to the germinal stage of embryogenesis.

A typical, unaffected germinal stage of embryo development can be characterized by fertilization, mitotic cleavage, morula formation, blastocyst formation, and implantation. Prior to fertilization, both the sperm and oocyte must travel to eventually reach one another in the fallopian tubes. The motility of sperm during this process is absolutely crucial for successful fertilization. Damage to the sperm can arise from a variety of sources, including inhospitable environments, physical stress from ejaculation, contractions of the uterine muscle, and mucosal secretions from the cervix. As a result, the number of sperm decreases from millions at the time of their ejaculation to mere thousands at their meeting with the oocyte in the fallopian tubes [2].

Prior to fertilization, there are two other key events that must occur for the unimpeded functioning of embryogenesis: sperm capacitation and the acrosome reaction. Sperm capacitation refers to the preparation, conditioning, and maturation of the sperm cells to travel through the female reproductive tract and fertilize an oocyte. Prior to the capacitation reaction, spermatozoa possess a high degree of motility but lack fertility. The process of sperm capacitation is characterized by several biochemical and physiological changes which culminate in a fertile spermatozoa. Some of these biochemical and physiological changes include a gradual increase in the extracellular concentration of calcium (Ca^{2+}) ions reflective of an internal cellular need for Ca^{2+}, a gradual increase in the extracellular concentration of sodium (Na^{+}) ions reflective of an

internal cellular need for Na^{+}, and an increase in the intracellular pH. Following sperm capacitation is the acrosome reaction, the second part of preparation in which an exocytosis reaction occurs to release the enzymes contained within the acrosomal membrane. Similar to capacitation, the acrosome reaction can also be characterized by certain biochemical and physiological changes including a rapid and substantial increase in the concentration of both Ca^{2+} and Na^{+} [3].

Along with interfering in the process of embryogenesis, another common way in which contraceptives exert their effects is through eliciting both physical and hormonal changes on the female reproductive system. The female reproductive system undergoes regular cyclic changes, referred to as the menstrual cycle. The menstrual cycle, like sperm capacitation and the acrosome reaction, can be characterized by numerous biochemical and physiological alterations [4]. At the cellular level, menstruation is largely regulated through hormonal signaling. Beginning in the hypothalamus of the brain, gonadotropin-releasing hormone (GnRH) is released beginning at the start of puberty. GnRH then stimulates the anterior pituitary, which in turn activates its G protein-coupled receptor (GPCR). This signaling of the GPCR induces the pituitary gland to then release two gonadotropins: follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH then travel to the ovaries where they stimulate the follicular cells, theca cells, and granulosa cells to produce key sex steroid hormones. Theca cells function to produce progesterone and androstenedione, the latter of which will diffuse into granulosa cells and be converted into testosterone and 17-β estradiol. Progesterone and 17-β estradiol constitute the primary governing hormones of the female reproductive system. At a larger physiological level, the menstrual cycle is split into four phases: menstruation, the follicular phase, ovulation, and the luteal phase. The levels of both estrogen and progesterone fluctuate throughout the menstrual

cycle; however, understanding why progesterone levels fluctuate is key to understanding the mechanism of most intrauterine devices. In the days prior to ovulation, progesterone levels remain relatively low. These levels will then drastically rise following the release of an egg as the female reproductive system thickens the uterine lining to prepare for potential implantation and pregnancy. This hormonal action forms the basis through which progestins function in contraceptives.

Mechanism of Action of Hormonal Intrauterine Devices

By far, the most common form of intrauterine contraceptive devices used among menstruating individuals in the United States are hormonal intrauterine devices (IUDs). These devices, marketed under brand names such as Kyleena, Mirena, Skyla, and Liletta, function primarily through the release of the synthetic hormone, levonorgestrel. For this reason, they may also be referred to as levonorgestrel-releasing intrauterine systems (LNG-IUS). These devices have two central mechanisms of action through which they prevent pregnancy: thickening of the cervical mucus and thinning of the endometrial lining. They have also been shown to partially suppress ovulation in some individuals; however, this is not considered one of their main mechanisms of action.

The basis through which levonorgestrel can elicit its contraceptive effect is through behaving as a progesterone agonist, also commonly referred to as a progestin. Specifically, levonorgestrel acts as a reversible, full agonist of the progesterone receptor. Unlike receptor antagonists, which bind to receptors and inhibit action, agonists are capable of interacting with receptors and eliciting a biological response. In the case of levonorgestrel intrauterine systems, the synthetic hormone is released in small doses at set increments of time—typically between 14 µg to 20 µg per day—and binds to the progesterone receptor. The basis through which

levonorgestrel is able to behave as a progesterone agonist lies in the structural similarity between the two molecules (Figures 1A and 1B). Specifically, levonorgestrel is a type of ethinylated derivative of progesterone referred to as a 13-ethyl gonane [5]. This classification comes in reference to the replacement of progesterone's methyl group of carbon 13 with an ethyl group. Additional differences between the two molecules contribute to the differentiation of levonorgestrel from other synthetic progestins.

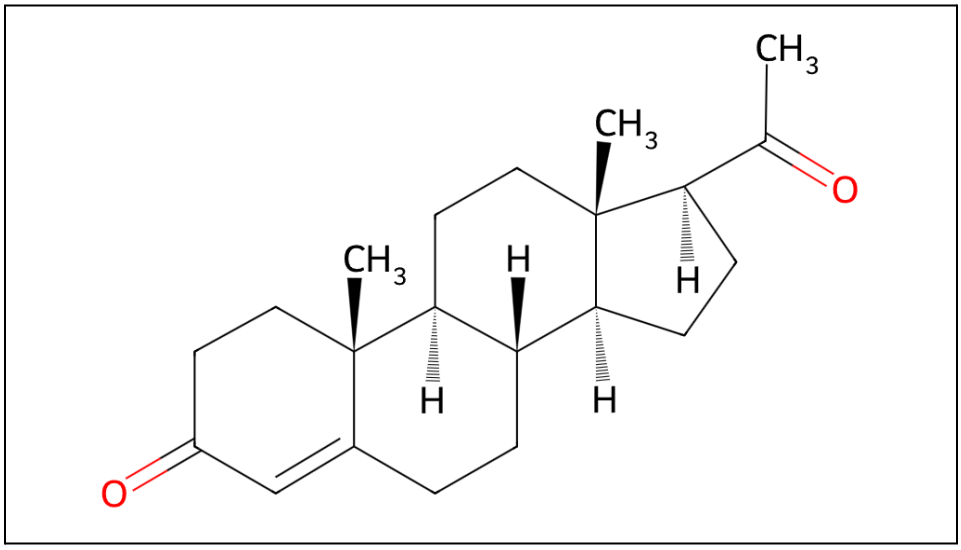

Figure 1A. The figure above, taken from reference *6*, displays the chemical structure of progesterone. Progesterone, naturally produced by the corpus luteum of the ovaries, differs from levonorgestrel at key points. The progesterone molecule contains methyl groups at C10 and C13, as well as an ethyl group at C17. The key structures conserved in both this molecule and levonorgestrel are the keto group at C3, the double bond between C4 and C5, and the gonane ring structure.

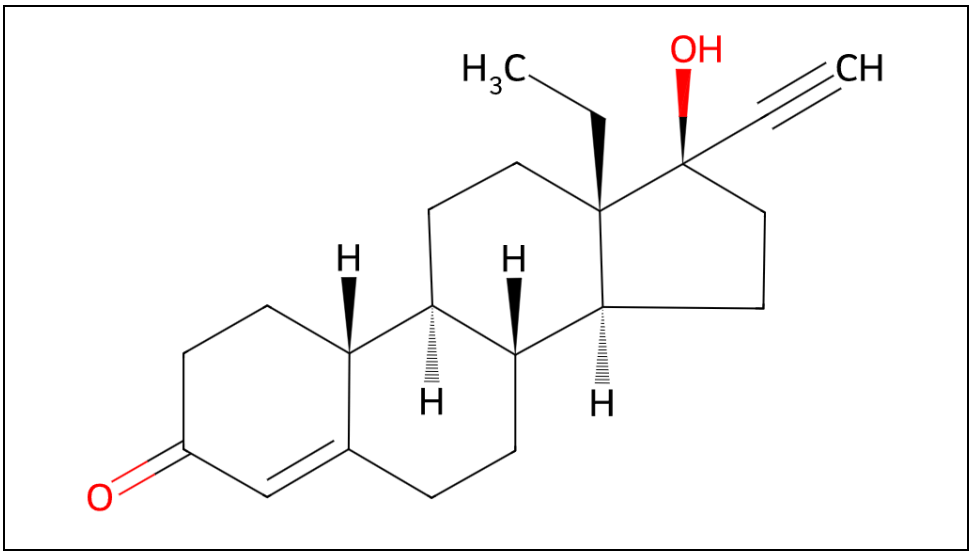

Figure 1B. The figure above, taken from reference *7*, displays the chemical structure of levonorgestrel. Levonorgestrel, a synthetically produced progestin, differs from progesterone at key points. The levonorgestrel molecule contains a lone hydrogen atom at C10, an ethyl group at C13, and both ethynyl and hydroxyl groups at C17. The key structures conserved in both this molecule and levonorgestrel are the keto group at C3, the double bond between C4 and C5, and the gonane ring structure.

The choice to use levonorgestrel in many hormonal intrauterine devices on the market today lies mainly in its binding affinity for the progesterone receptor. In one competitive binding study of norgestimate–a common progestogen—and its metabolites, as well as other well-researched synthetic and natural steroids to the human progesterone receptor, levonorgestrel showed the highest relative binding affinity (Figures 2A and 2B) [8]. In other words, lower concentrations of levonorgestrel were required to displace the ligand, H-R5020, compared to all the other steroids including progesterone itself.

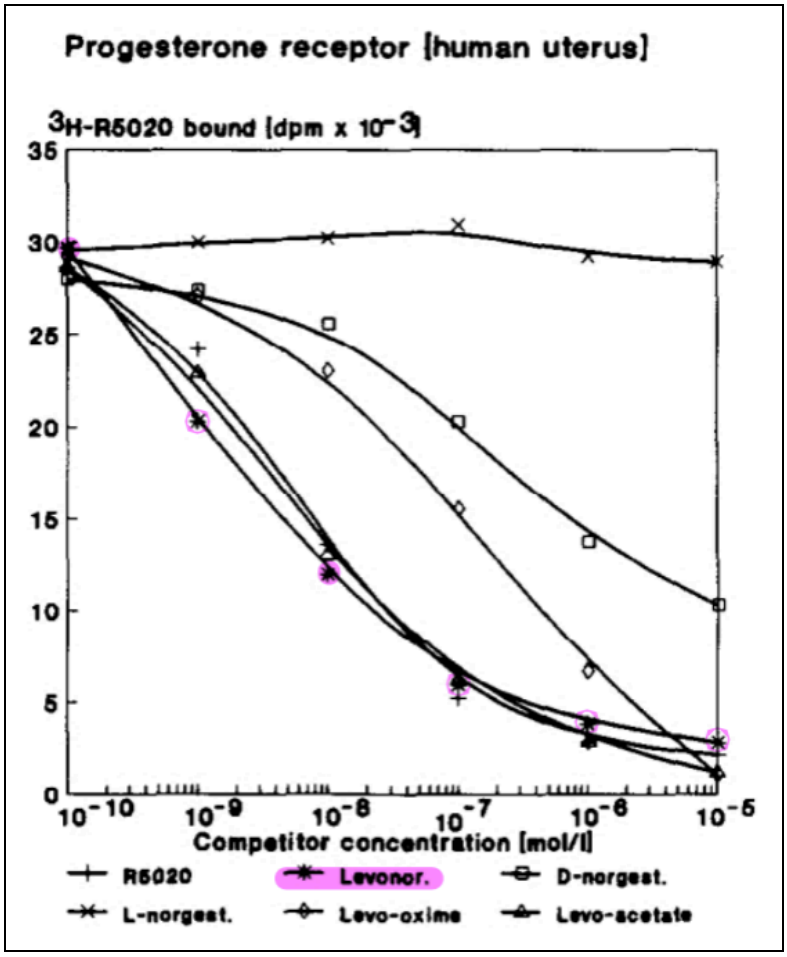

Figure 2A. The figure above, adapted from reference *8*, displays the relative binding affinities (RBA values) of various synthetic and natural steroids to the human progesterone receptor. Levonorgestrel, the main synthetic hormone utilized in most intrauterine devices, exhibits the highest binding affinity for the progesterone receptor of these steroids, made evident by its tendency to displace H-R5020 from the receptor at a lower concentration compared to that of the other steroids. It is this strong binding affinity that makes levonorgestrel a key component in intrauterine devices on the market today.

STEROID	PR	GR	MR	ER	AR	CBG	SHBG
Progesterone	30	12	100	< 0.1	< 0.1	< 0.1	53
Gestodene	70	18	280	< 0.1	86	< 0.1	40
R5020	100	17	53	< 0.1	< 0.1	< 0.1	< 0.1
Levonorges-trel	250	2.1	75	< 0.1	45	< 0.1	50
3-Ketodeso-gestrel	180	10	< 0.1	< 0.1	20	< 0.1	5
Desogestrel	1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
(L)-Norgestimate	0.8	6	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
(D)-Norgestimate	< 0.1	0.6	< 0.1	< 0.1	< 0.1	< 0.1	< 0.1
Levonorges-strel-17-aceta-te	110	5	80	< 0.1	40	< 0.1	< 0.1
Levonorges-trel-3-oxime	8	8	80	< 0.1	7	< 0.1	< 0.1

RBA values in % of reference steroid binding

Figure 2B. The figure above, adapted from reference *8*, displays the relative binding affinities (RBA values) of various synthetic and natural steroids to a variety of steroid receptors, most notably, the binding of progesterone and levonorgestrel to the human progesterone receptor. Levonorgestrel, the main synthetic hormone utilized in most intrauterine devices, exhibits a relative binding affinity for the progesterone receptor of 250% compared to that of progesterone itself at a mere 30%. It is this strong binding affinity that makes levonorgestrel a key component in intrauterine devices on the market today.

In contrast to when bodily progesterone binds to the receptor and induces thickening of the endometrial lining, levonorgestrel will bind to the progesterone receptor and alternatively induce thinning of the endometrial lining. This thinning of the uterine lining is unfavorable for eventual fertilization and implantation of an egg into the uterine wall, thus contributing to the overall contraceptive effect [9]. Additionally, binding of levonorgestrel results in an alteration to the molecular structure and viscosity of cervical mucus. This thickening of the cervical mucus contributes to highly limited sperm motility, ultimately creating an inhospitable environment for sperm and drastically decreasing the likelihood of successful fertilization.

The exact biochemical mechanisms occurring in the body to elicit these changes to the uterine lining and cervical mucus are not well understood or established; however, there are a number of possibilities currently being discussed within the scientific community. Studies focused on the release of levonorgestrel show a major suppressive effect on the concentrations of androstenedione and estradiol [10], the latter of which may have a direct mediating influence on the viscosity and overall production of cervical mucus [11].

Another possible biochemical target of levonorgestrel is insulin-like growth factor binding protein-1 (IGFBP-1). Expressed by endometrial stromal cells, IGFBP-1 is a crucial regulator of insulin-like growth factor 1 (IGF-1) which plays a key role in promoting endometrial decidualization to prepare the uterus for a pregnancy. One study found that in the endometrial samples of women undergoing continuous treatment with the levonorgestrel intrauterine system, expression of IGF-I mRNA became undetectable and levels of transcription decreased [12]. This is in direct contrast to IGFBP-I mRNA, which under the influence of this same treatment exhibited increased expression and transcription levels (Figures 3A and 3B). With this in mind, it is thought that suppression of IGF-I and activation of IGFBP-I by the LNG-IUS is likely a key mechanism through which levonorgestrel—and other synthetic progestogens—exert their antiproliferative, atrophic, and contraceptive effects on the endometrium.

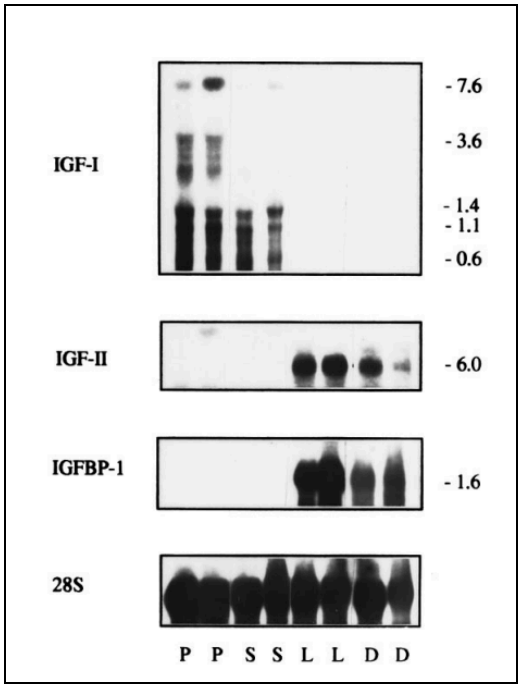

Figure 3A. The figure above, adapted from reference *12*, displays a Northern Blot analysis of the mRNAs encoding insulin-like growth factor (IGF)-I, IGF-II, and insulin-like growth factor binding protein (IGFBP)-I in the human endometrium during the proliferative (P) phase of the menstrual cycle, the secretory (S) phase of the menstrual cycle, during use of the levonorgestrel intrauterine system (L), and in early pregnancy decidua (D). Expression of IGF-I mRNA is demonstrated to be undetectable during use of the levonorgestrel intrauterine system, while expression of IGF-II mRNA and IGFBP-I mRNA are both detectable while under the influence of the levonorgestrel intrauterine system.

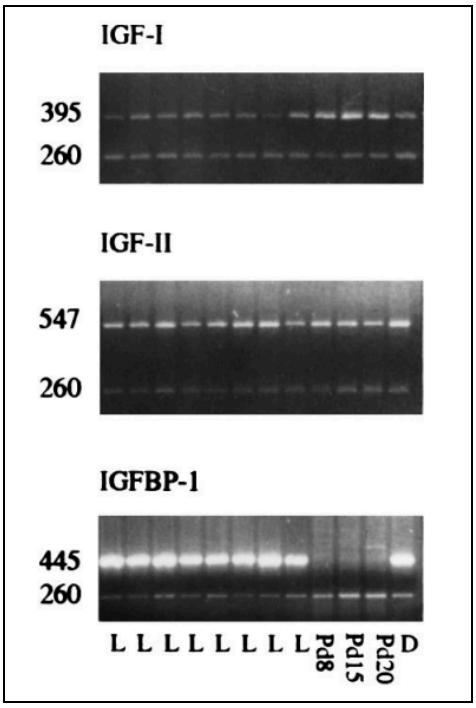

Figure 3B. The figure above, adapted from reference *12*, displays a Reverse-Transcriptase Polymerase Chain Reaction (RT-PCR) analysis of the amplification products of the mRNAs encoding insulin-like growth factor (IGF)-I, IGF-II, and insulin-like growth factor binding protein (IGFBP)-I in the human endometrium during the proliferative (P) phase of the menstrual cycle, the secretory (S) phase of the menstrual cycle, during use of the levonorgestrel intrauterine system (L), and in early pregnancy decidua (D). Under the influence of the levonorgestrel intrauterine system, both IGF-I mRNA and IGF-II mRNA demonstrated low levels of transcription. This is in contrast to the IGFBP-I which demonstrated increased transcription amplification during use of the levonorgestrel intrauterine system.

Mechanism of Action of Copper-Based Intrauterine Devices

Copper-based intrauterine devices (Cu-IUDs) are a common choice for individuals seeking contraceptive options that do not utilize hormones, with the most common of these devices going by the brand name ParaGard. Copper-based IUDs have two suspected primary mechanisms that work in tandem to impede fertilization and subsequent pregnancy. The first of these mechanisms is to induce an endometrial inflammatory response, effectively preventing

fertilization of the egg and later implantation of the egg to the uterine lining. The second of these mechanisms involves enacting a spermicidal effect that works to inhibit sperm motility, inhibit sperm capacitation, and block the acrosome reaction. The biochemical basis through which these mechanisms occur is still heavily disputed and not fully known; however, there are numerous promising possible explanations.

One possibility for how copper-based intrauterine devices function to induce these effects in the uterus and endometrium is through affecting the metabolism of endometrial cells. Studies have shown copper-based interference with the activity of enzymes involved in reproductive physiology such as carbonic anhydrases and alkaline phosphatases. Carbonic anhydrases are zinc-containing enzymes responsible for catalyzing the reversible conversion of carbon dioxide (CO_2) and water into soluble bicarbonate ($(HCO_3)^-$) and protons (H^+) [13]. This reaction is essential for a plethora of biological functions and in the maintenance of carbon dioxide levels in the body. In the female reproductive tract specifically, it acts to maintain uterine pH levels. A typical vaginal pH of 4.5 is expected for healthy women of reproductive age. Even slight alterations in this slightly acidic pH can greatly decrease fertility of the female reproductive system and lead to gestational complications. Further, the pH of the genital tract contributes to sperm capacitation, and as such, any aberrations will effectively impair this process [14]. The way in which copper ion release from Cu-IUDs can result in such pH alterations is through eliciting an antagonist effect on the concentration of zinc ions in the reproductive system. These zinc ions are critical to the enzymatic activity of the aforementioned carbonic anhydrase, thus any such decrease in the normal concentrations of zinc ions in the endometrial environment will result in inactivation of carbonic anhydrase activity. With this decreased activity comes

subsequent detrimental pH changes and is likely one of the ways in which Cu-IUDs alter endometrial metabolism to elicit their contraceptive effect.

Additionally, the introduction of copper-based intrauterine devices into the endometrial and cervical environment may play a key role in the significant increase in neutrophil, mononuclear cells, and plasma cells in the endometrium [15]. Specifically, the presence of high concentrations of leukocytes and macrophages in the endometrial environment and their subsequent cytotoxic effects. This accumulation of cytotoxic effects is often referred to as a foreign body reaction and is one of the many theories put forward as a likely contributor to the antifertility effect of not only Cu-IUDs, but of all intrauterine devices.

Diving a bit deeper into the biochemical changes that occur to elicit the contraceptive effect of Cu-IUDs, one study found two possible explanations. The first explanation ascertains that copper release in the uterus ultimately results in the scission of disulfide bonds contained in uterine proteins and mucins. Such a scission could reasonably be the driving force behind changes in the uterine lining that prevent implantation, changes in cervical mucus that create an inhospitable environment for sperm, and inactivation of the carbonic anhydrase and alkaline phosphatase as mentioned above. The second explanation postulates that the effectiveness of copper release in the uterus is the result of formation of cupric ions. This explanation lends to copper release causing inactivation of sperm and suppression of myometrial contractions [16].

The theory surrounding copper release leading to scission of disulfide bonds contained within uterine proteins and mucins is of particular interest as it relates to the findings of another study. This study found that when copper was introduced into the uterine environment it significantly decreased the binding ability of both the progesterone and estrogen receptors (Figure 4). Increasing the concentration of copper from just 10^{-6} M to 10^{-2} M reduced the

binding capacities of each receptor to nearly one-tenth of its original function. This is significant, as the steroid hormone receptor is known to possess some disulfide binding capacity. Thus, if copper introduction does lead to the scission of disulfide bonds within cervical mucus, it would be consistent with a subsequent inactivation of progesterone and some estrogen receptors. [17]

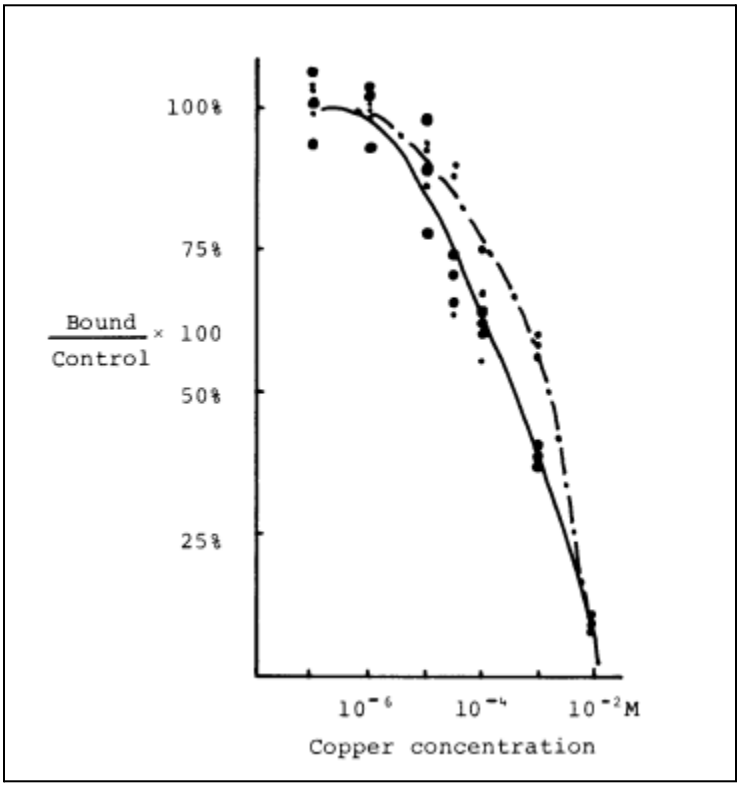

Figure 4. The figure above, adapted from reference *17*, displays the effect of copper on the steroid hormone-receptor binding ability of both the progesterone (straight line) and the estradiol (broken line) receptors. The introduction of copper concentrations as minimal as 10^{-2} M reduces the respective bindings capacities to 10% of their original function.

Intrauterine Devices: A Standout Contraceptive

Methods for preventing pregnancy are vast and extensive in range, and the number of sexually active women looking to reduce their chances of pregnancy is great. When selecting a method of reversible contraception, there are a number of factors to consider. Intrauterine devices set themselves apart from other contraceptive methods in both benefits and adverse effects.

The various methods of reversible contraceptives are commonly grouped into four categories: hormonal, nonhormonal, long-acting, and short-acting. Hormonal methods are those that elicit their effect through the release of steroid hormones such as progesterone or progestin, sometimes in conjunction with estrogen. Nonhormonal methods encompass any contraceptive methods that do not involve the release of these steroid hormones. This includes barrier methods like condoms and diaphragms, as well as the copper-bearing IUDs discussed in this paper. Intrauterine devices, along with implants, also comprise the long-acting contraceptive methods group. Short-acting methods include oral contraceptives, injections, and the previously mentioned barrier methods.

Modern intrauterine devices have become increasingly popular in the last 30 years for their most obvious benefit—not having to remember to take a pill every day. The levonorgestrel intrauterine device comes with its own advantages including its limiting pregnancy to less than 1 in 100 women per year, a return to typical fertility within 1 cycle after removal, and observed amenorrhea in around 40% of users two months after insertion. In some users, added benefits like period cramp reduction and significantly lighter menstrual periods were even observed. The copper-bearing intrauterine device is known for benefits such as highly effective rates with pregnancy occurring in only 1% of users per year, normal ovulation and menstruation cyclicity in

its users, and having no effect on long-term fertility following removal. Another added benefit of these copper-containing devices is that, if inserted within a certain time frame, they may also function as an emergency contraceptive [18].

However, intrauterine systems do not come without their own host of adverse effects. Copper-bearing IUDs have been known to exacerbate some of the less favorable aspects of menstruation by increasing the volume of blood dispelled, duration of bleeding, and discomfort felt during menses in users during the first 6 months of usage. Adverse effects of the levonorgestrel IUD include increases in the incidence of benign ovarian cysts, increased amounts of vaginal discharge, increased headache and migraine occurrences, acne, and symptoms of vulvovaginitis and other related vulvovaginal infections [18]. Possibly the most well-known adverse effect of all intrauterine devices, regardless of hormone content, is the discomfort and even severe pain experienced upon insertion in many users. Currently, the American College of Obstetricians and Gynecologists (ACOG) recommend practitioners inserting these devices offer patients local anesthetics like lidocaine spray, lidocaine cream, and paracervical blockage [18]. These local anesthetics, even in concurrence with over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs) taken prior to the time of insertion, are reported by many patients to still not be enough. As a result, many individuals seeking contraceptive options are wholly deterred from the idea of intrauterine devices as a result of anxiety surrounding possible pain and fear of their concerns being dismissed by clinicians.

Conclusion

The availability of a long-term, highly effective, and reversible method of birth control in the form of the intrauterine device has, without question, changed the lives of women across the globe. Furthemore, the invention of the copper-based IUD has provided an option to individuals

interested in the longevity and convenience of these devices but who may be deterred by the direct intervention of hormones. Current research surrounding intrauterine contraceptive systems provides great support for their effectiveness at preventing pregnancy, with some studies providing insight into their biochemical interactions in the body. Despite these studies and the extensive research into hormonal involvement in the body, there is still a vast knowledge gap where copper-based intrauterine devices are concerned. Our understanding of their interactions on a biochemical level are extremely limited and by extension, our understanding of how they cause certain adverse effects is limited. With a majority of the existing biochemical literature pertaining to trials with rats and mice, there is an immense need for clinical research that seeks to understand the biochemical effects in humans. Given the historical track record of medical research prioritizing men, it is unsurprising that there is so little insight into a contraceptive method used primarily by women. Even so, it is the time for change and for clinicians to fully understand what the devices they are inserting into patients actually do.

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