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The Mirena Migraine - A Review of the Pharmacodynamics of Levonorgestrel and Its Implications in Women's Health

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THE MIRENA MIGRAIN: A REVIEW OF THE PHARMACODYNAMICS OF LEVONORGESTREL AND ITS IMPLICATIONS IN WOMEN'S HEALTH

Honors Thesis

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Abstract

The new progestin, levonorgestrel, delivered via an intrauterine system or subdermal implant is showing promising signs of preventing pregnancy, decreasing excessive bleeding with menstruation, and returning fertility when removed (Backman, 2004). As promising as the levonorgestrel parental systems are, side effects are a common cause for concern and are a large reason for premature removal (Coukell & Balfour, 1998). Other than prolonged bleeding from insertion, and heavier periods for some women, other side effects have been observed such as weight gain, mood changes, dizziness and persistent, headache (Backman, 2004). With headache being one of the primary reasons for premature removal, previous literature has shown strong antiestrogenic activity among the pharmacodynamics of levonorgestrel (Schindler, 2003), which in turn may be the causative agent for the headache experienced among users.

Given that headaches are mediated by vasodilation and vasoconstriction, the antiestrogenic activity of levonorgestrel is hypothesized to affect estrogen mediated vasodilation (Schindler, 2003). As one of the strongest antagonist of estrogen, levonorgestrel has also been discussed to affect the oxidation of low-density lipoprotein (LDL) cholesterol impacting the endothelium of the cardiac vasculature (Zhu, Bonet, & Knopp, 2000). This review aims to identify how levonorgestrel could be the causative agent for the physiologic phenomenon of a headache experienced among users so that medical professionals and drug manufacturers can be guided towards developing and prescribing a more effective and tolerable birth control option.

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Introduction

For many women, the new Levonorgestrel Intrauterine device (LNG-IUD) has alleviated many of the struggles experienced from other forms of birth control. After a one-time insertion, the patient is up to 99.9% protected from pregnancy for up to five years (Backman, 2004). The patient is free from the hassle of remembering to take a pill every day, having to endure an intramuscular injection every three months, or having to worry about the potential failure of barrier methods. By preventing pregnancy for up to five years, the patient is essentially worry-free of an unwanted pregnancy, yet in the desire to get pregnant, the return to fertility after removal is almost immediate (Backman, 2004). In current studies additional benefits of the LNG-IUD include promising signs of protection against intrauterine cancers, endometriosis, dysmenorrhea, and menorrhagia (Backman, 2004). With a supposed low side effect profile, the LNG-IUD is becoming a popular choice for women when choosing a birth control method. While many women report satisfaction with the LNG-IUD, adverse reactions are being looked at to include prolonged bleeding from insertion, heavier periods for some women, in addition to weight gain, mood changes, dizziness and persistent headache (Backman, 2004).

Releasing only 20 mcgs of levonorgestrel (Backman, 2004), it has been noted that of the other hormonal birth control methods that also rely only on levonorgestrel as its birth control hormone (specifically the Norplant levonorgestrel releasing system implanted in the underside of the arm), they have also demonstrated a headache as being a prominent side effect (Coukell & Balfour, 1998). With levonorgestrel being the only hormone involved in these parental devices, this review aims to compare these parental

methods to combination levonorgestrel and estrogen oral contraceptives, and the copper

intrauterine device with no hormone involvement. Through comparison, it will be

investigated whether the levonorgestrel hormone itself is the causative agent for the

headache side effect.

In addition, this review will also look to identify how the pharmacodynamic

nature of levonorgestrel could produce a headache based on its antiestrogenic activity. By

identifying a possible link between the drug and its role in the headache, the implications

for this review are intended to promote healthcare professionals and drug manufacturers

to further investigate this particular side effect seeing that it is one of the leading causes

of premature removal (Coukell & Balfour, 1998). Given that 60% of LNG-IUD users

discontinue this particular birth control method before its five year duration, for

unexpected bleeding, pain and discomfort and progestogenic side effects which include a

headache (Ewies, 2009), future research is needed for a more tolerable birth control

option.

An Overview of the Natural Processes of the Menstrual Cycle

In the naturally occurring menstrual cycle, estrogen and progesterone are

responsible for the endometrial changes necessary to promote ovulation, fertilization,

implantation and fetal development. Day 1 of the menstrual cycle is marked by the onset

of menses where the endometrial lining is shed, along with the corpus luteum and the

unfertilized egg. The hormonal events that trigger menstruation are marked by declining

progesterone levels signaled by the decaying corpus luteum and unfertilized egg.

Following the decline in progesterone levels, the spiral arterioles and capillaries that

make up the uterine endometrial vasculature begin to degrade resulting in a release of

blood into the most superficial epithelium of the endometrium. In an effort to prevent

hemorrhage the arterioles contract and constrict. The blood generated from the

degradation and contraction of these arterioles further cascade the release of blood from

the most superficial endometrial vasculature resulting in menses (Elchalal & Abramov,

1995).

Following menstruation, the proliferative phase (days 7-14) begins as a response

to heightened estrogen secretion. Estrogen mediated, regrowth of the endometrial lining

occurs; endometrial mucosa thickens, glandular activity increases, and mitotic activity at

the basal layer is at an all-time high. The connective tissue of the endometrium known as

the stroma becomes more vascular as the constricted and condensed spiral arterioles

begin to elongate and re-perfuse the growing endometrial tissue. Nearing ovulation, the

endometrium gets thicker, more edematous in response to the heightened perfusion,

attracts white blood cells, and macrophages in order to prepare itself for a potential

implantation (Elchalal & Abramov, 1995).

Approximately mid-cycle (the 14th of a 28 day cycle), estrogen levels reach their

maximum prompting a surge of luteinizing hormone (LH) release from the pituitary

superseding ovulation. Once ovulation and the release of an egg from the follicle has

been achieved, estrogen levels begin to decline and progesterone levels rise. This period

marks the luteal phase of the menstrual cycle (Elchalal & Abramov, 1995). From

ovulation to approximately 72 hours after, the woman is now fertile and progesterone

levels continually rise. Rising progesterone is suggested to suspend the changes and

growth of the endometrium to promote implantation and resist overgrowth of the lining.

If fertilization is achieved and implantation occurs, the corpus luteum will persist on the ovary and continue its secretion of progesterone necessary to promote embryonic development and maintenance of the pregnancy. Should fertilization fail, the corpus luteum will degrade triggering the fall of progesterone that will again result in menstruation (Elchalal & Abramov, 1995).

The Impact of Levonorgestrel on the Body

Menstrual Cycle

Levonorgestrel is a synthetic second generation progestin designed to mimic the actions of naturally occurring progesterone. Levonorgestrel is successful in preventing pregnancy by thickening the cervical mucosa, suppressing the functioning of the endometrial lining, and working on the pituitary to suppress the LH surge (Coukell & Balfour, 1998). Producing the desired effects that make levonorgestrel successful in preventing pregnancy, there is a change in the woman's natural hormone levels as a result of levonorgestrel exposure. As discussed previously, natural progesterone is responsible for halting the continued growth of the endometrial lining. Progesterone achieves this by suppressing estrogen receptor gene transcription and ultimately estrogen receptor levels (Ewies, 2009). As a result, the endometrial lining is stunted in its growth because of the changes progesterone causes at the estrogen receptor site. Levonorgestrel, again created to mimic natural progesterone, achieves this change in estrogen receptor activity but is sought to be very antiestrogenic in its activity compared to other synthetic progestins (Ewies, 2009). What makes levonorgestrel antiestrogenic is its androgenic effect as an antagonist to estrogen. Natural progesterone and progestins alike directly affect normal

functioning hydroxysteroid dehydrogenase (HSD); HSD-2 is an enzyme whose type 2

form deactivates estrogen (E_2) to a weaker form (E_1). When progesterone levels are

heightened, HSD-2 enzymatic activity increases, churning out more weakened estrogen

(Guttinger & Crtichley, 2007).   The lack of strength in endometrial estrogen is

hypothesized to weaken the endometrial blood vessels resulting in the break through

bleeding that is experienced by users the first few months after insertion (Guttinger &

Critchley, 2007). Keeping in mind that endometrial blood vessels may be affected by this

change in estrogen strength, what may be the systemic effects of a weaker estrogen

outside the endometrial cavity, under the influence of levonorgestrel? Ovulation for one,

mediated by estrogen levels, appears to possibly be affected.

Blood Serum Concentrations and Ovulation

With the use of the LNG-IUD, it is shown that ovulation is not inhibited in *most*

women (Backman, 2004). On the other hand, use of the LNG-IUD produces

symptomatology comparable to menopause in 50% of the women treated (Ewies, 2009).

Similarly, studies suggest that 50% or more of the users treated with levonorgestrel

subdermal devices do not ovulate (Coukell & Balfour, 1998). The difference in ovulatory

versus annovulatory cycles in users may lie in the serum levels of levonorgestrel

dependent on body weight. In subdermal levonorgestrel devices, for a person weighing

>70 kg, serum levonorgestrel levels are decreased by 0.0033 mg/L/kg. In comparison to

serum levels of users >70 kg, users who weighed <50 kg had 45% higher serum levels of

levonorgestrel (Coukell & Balfour, 1998). Designed to secrete only 20 mcg/day of

levonorgestrel continually from a 52 mg reservoir (Selim & Hussein, 2013), if body

weight dependent, it may be possible that more than 20 mcg are released in women of

smaller body composition, and some evidence suggests this. Blood serum levels of levonorgestrel is found to vary among users despite alternative research suggesting that serum levels generally stay within 150-200 pg/ml (Guttinger & Critchely, 2007). Alternative studies also suggest that 85% of LNG-IUD users are still ovulatory and that serum levels high enough to inhibit ovulation would require a daily release of at least 50 mcg (Guttinger & Crtichely, 2007). If the LNG-IUD releases 50 mcg (2.5 times more than intended at 20 mcg) through simple mathematics we should expect the serum levels to therefore be between 375-500 pg/ml. For comparative assay, the serum levels to which levonorgestrel is suggested to stay, 150-200 pg/ml, is equivalent to 550.65- 734.2 pmol/L. In Table 1, it is apparent that four out of six studies presented in his table show serum levonorgestrel levels reaching higher than 734.2 pmol/L $\approx$ 200 pg/ml. Three of the studies even show levels high enough to inhibit ovulation with serum levonorgestrel

Table I: Serum Levels of LNG in Users of the LNG-IUD
The reported steady state serum levels of levonorgestrel in users of
LNG-IUS and 30 mg levonorgestrel only pill.
Study Levonorgestrel serum level (pmol/L)

Levonorgestrel 30 mg pill

Weiner et al. [25]	800

LNG-IUS

Ratsula et al. [26]	455
Suhonen et al. [27]	480–640
Lockhat et al. [9]	1062
Nilsson et al. [28]	640–1601
Xiao et al. [29]	960–1601
Raudaskoski et al. [20]	1504

*LNG-IUS, Levonorgestrel-releasing Intrauterine System.

Ewies, A. A. (2009). Levonorgestrel-releasing Intrauterine System - The discontinuing story. Gynecological Endocrinology, 25(10), 668-673.

Accounting for the variable serum levels, body weight is not the only influential factor. The metabolic rate and clearance rate of levonorgestrel has been found to be very different in users by at least several-fold (Ewies, 2009). Variations in serum levels are suggested to be reflective of the differences in metabolism and responses users may have to levonorgestrel (Ewies, 2009). The pharmacodynamics of levonorgestrel from user to user varies, regardless of whether levonorgestrel is parenteral or enteral in form. This raises the question as to what the impacts are, if any, levonorgestrel could have on the cardiovascular system outside the endometrium of the uterus if serum concentrations are not as expected. Does this have anything to do with the headache experienced among users? Perhaps.

Oxidation of LDL-C by Levonorgestrel and Its Potential Impact on Cardiovascular System

Studies suggest that levonorgestrel implants do not significantly affect the lipid profile of users (Sivin, 2003). Research mentions a slight decrease in the total cholesterol level and triglyceride level in the first month of use, with levels returning to baseline shortly thereafter (Sivin, 2003). Given that the serum levels of the LNG-IUD is at its highest in the first month of administration, a decrease in the lipid profile values may not be coincidence. Naturally occurring estrogen has been shown to elicit an antioxidant effect on the lipids circulating throughout the body as it protects low density lipid cholesterol (LDL-C) molecules from being oxidized (Zhu et al., 2000). Oxidized LDL-C has recently been recognized as a contributing factor in the pathogenesis of

atherosclerosis. Oxidation of LDL-C induces the release of inflammatory chemicals by the endothelial walls of the cardiac vasculature, the inhibition of the production of nitric oxide responsible for vasodilation, and the formation of Foam Cells—the distinctive marker of atherosclerosis because their death is what is responsible for the formation of plaques in the arterial walls (Ruiz-Sanz, Navarro, Martínez, Hernández, Matorras, & Ruiz-Larrea, 2007).

In a study done by Zhu et al., 2000, LDL molecules were extracted from the plasma of fasting, healthy donors, not on hormone therapy. Their plasma was then subjected to three progestins: norgestimate, levonorgestrel, medroxyprogesterone acetate (MPA); estrogen, 17β-estradiol (E_2); and progesterone under oxidation inducing conditions. While 17β-estradiol, showed a protective effect by inhibiting LDL-C oxidation, the progestins were shown to promote its oxidation in a dose-dependent pattern. Estrogen even in combination with the progestins still showed that the progestins inhibited the protective effects of the estrogen. Of all the progestins used in the study, inhibition and enhanced cytotoxicity was greatest with the use of LNG and MPA. This study continues to discuss the importance of LDL oxidation by these two progestins and its importance if not balanced by antioxidants. The consequences include the development of vascular conditions including atherosclerosis, vasospasm, and activity of arterial protein kinase C activity (a molecule that plays a role in irritating the blood vessels causing vasospasm, constriction and potential chronic contraction of the arteries [Laher & Zhang, 2001]), (Zhu et al., 2000). While it is known that levonorgestrel lacks the protective antioxidant structures found in estrogen, it is not known why or what in the levonorgestrel hormone molecule promotes LDL-C oxidation (Zhu et al., 2000).

Another review promotes that the LNG-IUD can be used in women who have a cardiac history of embolisms, it decreases the resistance of activated protein C activity (a marker for inflammation), and cites one study in which Asian women using the LNG-IUD saw a small decrease in their total cholesterol profiles (Mansour, 2012). In another study done in 2010, 44 women with endometriosis were comparatively treated with the LNG-IUD and a GnRH analogue (GnRHa) while their lipid levels in conjunction with other cardiac markers were monitored (Ferreira, Vieira, Rosa-e-Silva, Sá Rosa-e-Silva, Nogueira& Ferriani, 2010). While the subjects activated protein C (APC) decreased, concurrent with the previously mentioned study, there was also a significant decrease in their lipid profiles. Table 2, shows that the results demonstrate a significant decrease in total cholesterol, trigylcerides, LDL cholesterol, and HDL cholesterol after

six months.

Table 2: Lipid Profiles of Users with the LNG IUS and a GnRHa

(Data are reported as means±SD; p<.05 compared to pretreatment; T p<.05 for comparison of posttreatment results.)

	LNG-IUS (n=22)		GnRHa (n=18)	
	Basal	6 months	Basal	6 months
TC (mg/dL)	242.3±82.2	180.8±31.6 τ	228.6±57.7	223.5±58.4τ
TG (mg/dL)	115.3±75.8	85.5±41.2 τ	128.9±91.4	149.2±76.9τ
LDL-C (mg/dL)	158.7±65	115.6±25.3 τ	142.7±40	138.9±42.8τ
HDL-C (mg/dL)	60.5±19.3	47.9±10.8	60±15.6	54.7±16.6

Ferreira, R., Vieira, C., Rosa-e-Silva, J., Sá Rosa-e-Silva, A. J., Nogueira, A. A., & Ferriani, R. A. (2010). Effects of the levonorgestrel-releasing intrauterine system on cardiovascular risk markers in patients with endometriosis: a comparative study with the GnRH analogue. Contraception, 81(2), 117-122.

Reduction in the Lipid Profile

Given that the LNG-IUD is often prescribed for women with endometriosis, it is difficult to discern what is actually happening to cause the decreases seen in the lipid profile. The liver is most likely participatory in the removal of the cholesterol from the body, but does some of it oxidize? When evaluating the greatest decrease in the separate lipid levels themselves (TG, LDL, HDL) in this particular study, LDL-C levels decreased the most with an average decrease of 43.1 mg/dL. In addition to LDL-C reduction, unfavorable decreases were seen in the HDL cholesterol levels, adding to the perceived cardiovascular risk of the LNG-IUD because of HDL cholesterol's importance in protection against heart disease (Ferreira et al., 2010). This study suggests that the decrease in LDL-C is favorable for the LNG-IUD user because with less LDL-C circulating there is less to be oxidized (Ferreira et al., 2010), however the risk of it being oxidized, if it is in fact being oxidized, is heightened due to the lack of antioxidant protection of estrogen because of its antagonism by levonorgestrel.

While this particular study had a small sample size, it raises importance questions and concerns. Is there perhaps something in the pathogenesis of endometriosis that may cause the body to respond to levonorgestrel in this particular way? Or does this suggest a phenomenon such as lipid oxidation as discussed prior which will increase cardiovascular risk for any user? And lastly, is this phenomenon only occurring in some but not all women? While more research is needed to identify and answer these questions, this particular study discusses the variability of the lipid profile in users of the LNG-IUD seen in other research (Ferreira et al., 2010). Citing six different studies, this article discusses that a decrease is seen in all aspects of the lipid profile among normal women (without

uterine and menstrual abnormalities); citing another study, this article discusses that in

normal women HDL and TC levels decreased with no mentionable decreases in TG or

LDL levels; and citing three other studies, these particular articles mention that no

changes in lipid profiles were observed, and that even an increase in HDL cholesterol can

occur (Ferreira et al., 2010). With such variability in lipid levels among users, it would

come as no surprise if there was perhaps a relation to the variability in the serum levels

seen in users with the LNG-IUD.

LDL-C, LNG-IUD, and the Potential Relationship to Migraines and Headaches

In the United States, 43% of women are affected by migraines with the prevalence

of migraines increasing with age (Edlow & Bartz, 2010). Most studies that investigate the

reasons for discontinuing the use of the LNG-IUD or other parental levonorgestrel

implants use *headache* as a category. However, most have not broken this category down

into the specific types of headaches (i.e. tension, migraine, cluster, etc.) that are occurring

(Coukell & Balfour, 1998; Daud & Ewies, 2008). The LNG-IUD is contraindicated in

those who have migraines to begin with (Willet, 2009), and in the informational packet

that is distributed with the LNG-IUD it is suggested that the user go immediately to their

doctor if they experience an increase in persistent headaches or a migraine for the first

time (Willet, 2009). Considering this, perhaps there is a causal relationship not yet

understood.

In the New Drug Application submitted to the FDA in 2009 for the Mirena®

LNG-IUD, the medical officer's additive comment stated that a headache as one of the

top three non-serious adverse events, is *possibly* related the LNG-IUD (Willett, 2009). In

one study presented in the application, a list of treatment-emergent adverse events were

reported with headache being the most prevalent adverse event with 13% of 80 subjects

experiencing a headache. In comparison to medroxyprogesterone acetate (MPA), a third

generation progestin with similar antiestrogenic effects but to a slightly lesser extent (Zhu

et al., 2000), only 9% of 82 subjects experienced a headache (Willett, 2009). While there

seems to be an absence of literature to my knowledge, concluding whether or not the

prevalence of headache is associated with the strength of the antiestrogenic activity of the

progestins used in progestin-only birth control methods, its possibility should not be

overlooked.

Given that evidence that levonorgestrel has been seen to promote oxidation of

LDL-C, it might not be coincidence that the results and by products of LDL-C oxidation

could contribute to a headache or a migraine considering vasospasm, and the release of

inflammatory chemicals occur with LDL-C oxidation. Diagnosis of migraines in clinical

practice relies on a throbbing pain as the major symptom of migraine headaches (Edlow

& Bartz, 2010). However in recent literature, a migraine is no longer suspected to be due

to vascular condition)Gruber, Bernecker, Pailer, Lechner, Horejsi, Möller, & Truschnig-

Wilders, 2010). Instead, it is supposedly a neurological condition in nature with vascular

complications, especially ischemic stroke (Gruber et al., 2010). LDL-C oxidation is an

independent risk factor for atherogenesis because of its molecular strength and its ability

to cause vascular dysfunctions through the production of free-radical oxygen formation,

tissue remodeling, and induction of oxidative stress on the body. In the pathophysiology

behind migraines, there is strong evidence that oxidative stress plays a role in their

development (Gruber et al., 2010). In two studies, LDL-C was significantly increased in those who experienced migraines regardless of BMI (Gruber et al., 2010; Bernecker, Pailer, Kieslinger, Horejsi, Möller, Lechner, & Gruber, 2011). Given that LDL-C oxidation is an independent risk factor for cardiovascular complications including migraines, the risk of developing atherogenic and harmful cardiovascular changes in the body may perhaps still be present even in the absence or improved atherogenic profile from use of the LNG-IUD.

LDL-C Oxidation and Nitric Oxide Inactivation

While it is not known how levonorgestrel promotes LDL-C oxidation, it is interesting to note that oxidative stress impacts the beneficial effects of nitric oxide (NO) (Bernecker et al., 2011), a chemical also partly mediated by estrogen. NO is responsible for: inhibiting platelet function, inhibiting the aggregation of inflammatory cells, promoting enzymatic fibrinolysis of clots, weakening endothelial smooth muscle proliferation, and vasodilation (Bernecker et al., 2011). Estrogen stimulates the production of nitric oxide by stimulating neuronal nitric oxide synthase (nNOS) which impacts the nervous system. This in turn produces and impacts endothelial nitric oxide synthase (eNOS) production in the cardiovascular system (Lekontseva, Chakrabarti, Jiang, Cheung, & Davidge, 2011). Given that migraines are both neuronal and vascular in nature, perhaps changes in serum estrogen or its strength is the link to the female migraine and the reason why migraine occurrence is three times higher in post-pubertal females compared to males (Edlow & Bartz, 2010). Not only is estrogen protective against atherogenesis, it also promotes regrowth of damaged endothelium, regulates pain

perception and regulates endothelial muscle tone (Ashkenazi & Silberstein, 2006).

Estrogen receptors are also found in both cardiac cells and vascular cells (Tarhouni,

Guihot, Freidja, Toutain, Henrion, Baufreton, & Henrion, 2013).

It is not known whether or not the antiestrogenic activity of the levonorgestrel

molecule impacts the nitric oxide production that estrogen regulates because of its

antagonism. Nor is it known whether or not the impact of levonorgestrel on the HSD-2

enzymatic activity producing a weaker estrogen is responsible for many of the

pro-oxidant activities in the body in conjunction to a change in NO production. Keeping

in mind that the products of LDL-C oxidation known to be caused by levonorgestrel can

inactivate NO (Bernecker et al., 2011), produce inflammatory chemicals, and cause

vasospasm, levonorgestrel very well may be the causative agent for the headache or

migraine developed or exacerbated in users as the FDA's medical officer suggested, and

carry a potential cardiac risk as well.

Comparison of the LNG-IUD and the Copper IUD in Headache Frequency and Risk for

Atherosclerosis

Because migraines with and without aura (a visual and auditory component to

symptoms) can contribute to ischemic strokes, the World Health Organization has rated

each birth control category for clinical practice either a category 1, 2, 3, 4 in regard to

headaches. While the copper IUD has been rated a category 1, meaning that there are no

contraindications for a specific condition or set of conditions [headache] that would

otherwise raise alarm, the LNG-IUD and other progestin only birth control methods

(IUD, IM injections, pills) are given a category 2 (Harris & Kaneshiro, 2009). Category 2

indicates that the particular birth control method can be used; however, careful observation of the patient must occur. Although the progestin only methods are ranked higher, in order to begin to assess and possibly single out levonorgestrel as the cause of the headache developed among many users, more research needs to be conducted. Most literature suggests variability in the lipid profiles among LNG-IUD users. When comparing lipid profiles of the LNG-IUD against those in users of the Copper-IUD, there is no significant difference in the lipid profile (Ng, Liang, & Singh, 2009) or the occurrence of headaches (Suhonen, Haukkamaa, Jakobsson, & Rauramo, 2004). While studies suggest that a favorable lipid profile is being seen among users of both the Copper-IUD and the LNG-IUD, regardless of the number of circulating lipid molecules in the blood, it is the size of lipid molecules that is an important factor in the development of atherosclerosis, not necessarily the number (Ruiz-Sanz et al., 2007). In lieu, despite having a favorable profile, it is not favorable if oxidation is occurring and it is not being detected because research is only looking at the number and not the size of the LDL-C molecules. The consensus is that individuals with small, dense LDL-C molecules are more at risk for the development of atherosclerosis, and that those with large LDL-C molecules are found in those who are healthy with a normal BMI (Manning, Edwards, Wagner, Wagner, Adams, & Parks, 1997).

However, in an interesting study done on Cynomolgus Monkeys who were fed an atherogenic diet, and subject to estrogen (EE) alone, EE+LNG in combination, and LNG alone, it was demonstrated that exogenous hormones affect LDL-C size and density (Manning et al., 1997). Although treatment with EE and EE+LNG resulted in smaller, more dense, LDL-C molecules, the molecules contained less cholesterol, less

apolipoprotein E (a molecule responsible for carrying cholesterol in the bloodstream), and reacted less with arterial proteoglycans (the molecule that LDL-C and apolipoprotein E fuses to in the arteries to form plaques) (Manning et al., 1997). LNG alone, although producing a larger LDL-C molecule, reacted more with the arterial proteoglycans. The authors of this study suggested that in women, smaller LDL-C molecules do not increase their risk for the development of atherosclerosis (Manning et al., 1997). More recent literature suggests the opposite, in that smaller LDL-C molecules are subject to oxidation more so than larger LDL molecules (Ruiz-Sanz et al., 2007).

Not only does LNG induce LDL-C oxidation, but interestingly enough copper does as well, and is one the substances used to promote LDL-C oxidation in laboratory testing (Chiang, Parthasarathy, & Santanam, 2004). Is it coincidence then that both substances show almost equal lipid profiles and headache frequencies in users? Perhaps not.

Conclusion & Suggestions for: Future Research, Prescribers, and Pharmaceutical Companies

Considering that neither birth control method contains any estrogen, more research needs to be conducted to find out whether slow atherogenic changes are occurring and whether a headache is an indicator. When assessing whether these atherogenic changes are occurring, research needs to focus on LDL-C size instead of number. Although a decrease in the lipid profile is favorable, if there are any atherogenic changes occurring regardless, the user has a right to know, and the provider should be aware of it and forewarn his/her patients. The provider should also take the complaint of

a headache as an indication that something more serious may be occurring and consider

the removal of the LNG-IUD. While the LNG-IUD is still a very good and beneficial

birth control for many, there is still room for improvement. Given that LNG is one of the

most pro-oxidative progestins available, and that the amount of hormone released from

the LNG-IUD reservoir is variable and dependent on BMI, metabolic rate, and individual

clearance rate (Ewies, 2009), in order to reduce atherogenic risk in users, perhaps a less

pro-oxidative progestin IUD can be used, with different doses of the hormone available

based on weight.

The doses available should correspond not only to the patient's weight, but also to

the patient's condition(s), if any, that would also warrant the placement of an IUD. For

instance, if there is a cancer present in the endometrium, higher doses of the progestin

IUD, or the LNG-IUD would be prescribed as long as the benefits outweigh the risks. In

healthy premenopausal women of normal BMI, the lowest dose of the progestin IUD

should be prescribed. The hormone and its dosage should be enough to protect against

pregnancy, dysmenorrhea, and menorrhagia, but should not exceed the total amount of

circulating estrogen. While there are less pro-oxidative progestins available, there still

may be a small risk of contribution to atherosclerosis, however, as long as estrogen is

available to exert its antioxidant effect, it can help combat its development. More

research would need to be conducted on which progestin achieves the same benefits as

the LNG-IUD, but with a lesser risk of contribution to atherosclerosis. By using a

different progestin, it may provide for a better, more tolerable birth control option that is

tailored to the user, thereby contributing to the minimization of the progestogenic side

effects and a headache that is experienced among many users and a reason for premature

removal.

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