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Abstract

With every medication there are risks and benefits. Most realize that with every desired benefit a medication provides the individual may also experience side effects. These side effects may have a negative or positive impact on the individual's overall health and wellbeing. I researched and performed a textual analysis of the scientific literature and data regarding the risks and benefits of combined oral contraceptive pill use in adolescent and young women. Following the completion of this research, an attempt was made to synthesize the overall message surrounding oral contraceptive use in adolescent and young women. The combination pill contains both a synthetic estrogen and progesterone, also known as progestogen, with estrogen doses varying from 20-50 μ g and progesterone varying from first to fourth generation progestogens. The pill works by introducing these hormones into the body and suppressing the body's natural fluctuations of hormones throughout a woman's menstrual cycle. Estrogen has been known to affect ocular health and vascular function, as well as an individual's risk for cancer. As a result, combined oral contraceptives have been linked to an increased risk for stroke, cardiovascular issues, asthma symptoms, and breast cancer. That being said, the combination pill has also been proven to provide many benefits. Aside from preventing an unwanted pregnancy, oral contraceptive use has been shown to effectively treat acne, menstrual irregularity, and polycystic ovarian syndrome symptoms, as well as decrease an individual's risk for endometrial and ovarian cancers. All of these risks and benefits may be influenced by numerous factors. Therefore, it is important for medical care providers to take a patient's medical and personal history into account prior to making a decision on whether or not to prescribe the combination pill to an individual.

Introduction

With any medication there are risks and benefits. These risks and benefits may vary depending on factors such as the medication being taken and the genetic makeup of the person who is taking it. Different people may experience different effects, with effects varying from one or two small, almost unnoticeable side effects to an entire array of complications and issues. Others do not seem to be affected at all. One such medication that comes to mind when considering these types of effects is birth control, specifically hormonal oral contraceptives.

Hormonal oral contraceptives contain a synthetic estrogen and a progestogen. Pills vary by the amount of estrogen they contain, as well as the type of progestogen (Hatcher, 2009, 194). High-dose pills contain up to 50 μ g of estrogen, while moderate-low doses fall somewhere under 35 μ g per pill. Progestogens may be first, second, third, or fourth generation, depending on when they were introduced to the market as part of the contraceptive pill. First-generation progestogens include norethindrone and ethynodiol diacetate. Initially, high concentrations of these hormones were combined with high doses of estrogen (Hatcher, 2009, 193). Second-generation progestogens include levonorgestrel, norethisterone, and norgestrel. Third-generation progestogens include norgestimate, gestodene, and desogestrel. Fourth-generation progestogens include ethinyl estradiol and drospirenone (Hatcher, 2009, 195-6). Progestogens can also be prescribed independently in pills containing no estrogen.

The combination pill contains both estrogen and progestogen and works by suppressing the levels of reproductive hormones, such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), estrogen, and progesterone in the female body (Hatcher, 2009, 197). The synthetic estrogen and progestogen from the pill travel directly to the pituitary gland and prevent the release of LH and FSH and ultimately keep the levels of estrogen and progesterone being

produced by the body at a constant level rather than allowing those levels to fluctuate, as they would throughout a normal menstrual cycle (Hatcher, 2009, 197). In women who do not use hormonal birth control, the fluctuations of these hormones triggers ovulation, egg maturation and release; they also play various other roles in menstruation and pregnancy (MacGregor, 2006, 53). The introduction of estrogen and progestogen hormones into the body through birth control inhibits the body's natural ovulation cycle through a negative feedback mechanism, thus preventing an unwanted pregnancy (Hatcher, 2009, 197). Synthetic estrogens have also been shown to regulate bleeding, alter secretions, and alter cellular structures of the endometrium (Hatcher, 2009, 206). Progestogens work by thickening the cervical mucus, making it much harder for sperm to travel, and thus making it less likely that the sperm will come in contact with an egg (MacGregor, 2006, 53). All of these effects in combination are very effective in preventing pregnancy.

Progestin-only pills introduce the synthetic progesterone, one of the previously mentioned progestogens, into the body in the absence of a synthetic estrogen. This pill works by causing the cervical mucus to thicken, which makes it difficult for sperm to enter the uterus to reach the egg (MacGregor, 2006, 57). Similarly to the combination pill, it can inhibit the natural ovulation cycle, but it has not been shown to do so in a consistent manner.

Due to the combination oral contraceptive pill containing both synthetic hormones and preventing pregnancy by inhibiting normal bodily processes, this analysis will focus on the risks and benefits of the pill, specifically the effects on adolescents and young women.

As the combination birth control pill blocks the ovulation cycle and therefore, the release of the egg, it is effective in preventing pregnancy (MacGregor, 2006, 53). Given this

information, it raises the question: Is it a good thing to alter the body's natural processes and what are the risks and benefits associated with doing so?

Unfortunately, there is likely no right or wrong answer to these questions. For many women, hormonal birth control relieves severe premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD) symptoms. That being said, all women are different and each medication may affect them differently. An individual's genetic makeup, family history, and medical history are just a few factors that may influence how her body reacts to hormonal contraception. There is an abundance of information available to the public regarding the typical side effects of birth control pills, from nausea, headaches, bloating, weight gain, and breast tenderness to decreased libido, vision changes, and depression. Benefits include the regulation of the menstrual cycle, prevention of an unwanted pregnancy, and the treatment of acne and endometriosis. But how much is the general public unaware of and why do oral contraceptive pills have these effects?

Ultimately, the goal of this research is to uncover some of the answers to these questions and also to develop a better understanding of the message surrounding the data on the combined oral contraceptive pill use. It must also be taken into consideration that each culture has its own beliefs and opinions regarding contraception and pregnancy.

Methodology

The first step in completing this project was researching the risks and benefits of oral contraception in order to understand what research has been conducted and what information is available. The intended audience of each of these research papers was then determined. The

intended audience not only varies from culture to culture, but also has an effect on the overall message being presented by the researcher or author of the paper.

The next step was to perform a textual analysis of the papers, including the data surrounding the risks and benefits of oral contraception on adolescents and young women and the manner in which that data is presented. The hope was to bring together information from scientific articles into one paper and ultimately present the author's primary messages and what implications these conclusions have for society as a whole. Specific criteria were used to locate articles for this research. Databases consulted included the following: PubMed, BioMed Central, MEDLINE (EBSCO), which incorporates several databases into a single search, Proquest nursing and allied health database, ResearchGate, and Web of Science. Key words that were used included: "young women", "oral contraceptives", "oral contraception", "effects", and "benefits". The use of just one of these terms resulted in hundreds or even thousands of articles in return, and as a result, several of the above terms were used in conjunction. Whether or not to include or exclude an article depended on the intended audience and whether the article was pertinent to my research, a primary source, and presented research that was performed properly and provided clear results.

In many cases, while searching for information, the results yielded from the search contained the key words, but the article ultimately did not pertain directly to the research being conducted. Those articles were excluded. The majority of the information for this project was obtained from primary sources. Secondary sources and reviews were used for clarity and to help locate additional information. The majority of this research focused on American and European cultures with other cultures excluded. However, in several instances research from other

countries was used to compare findings. This project focused on the data surrounding only the combination pill, so all articles regarding the progestin-only pill were excluded.

The message which authors present with their data could vary depending on the culture or society that the data is being presented to. An attempt was made to obtain a clear, central message about how American and European societies view oral contraception. This was completed through textual analysis and comparison of numerous articles. The complete analysis was conducted by breaking down the text to look for common phrases or words, determining the underlying tone of the article, and simplifying the data into major categories.

Findings

Despite how much is already known, there is just as much that is unknown. However, the combination pill and its effects are being researched and new discoveries are constantly being made. Montoya and his colleagues at Utrecht University have shown that oral contraceptives may have an impact on social-emotional behaviors and brain function, particularly in young women whose brains are still developing (2017).

Estrogen and progesterone are known to have an impact on brain development and also on certain regions of the brain, such as the amygdala, hypothalamus, and hippocampus. All of these regions play a role in social-emotional behavior (Montoya, 2017, 125-6). The pill introduces synthetic estrogen and progesterone hormones into the body and by negative feedback decreases the body's release of these hormones. Decreasing these levels has implications in behavioral changes, as well as in structural changes in the brain (Montoya, 2017, 126). This would particularly influence the developing brains of young women.

Furthermore, estrogen has been shown to reduce fear, particularly through a process of fear extinction while progesterone is known to help reduce stress and anxiety and plays more of a role in emotional response (Montoya, 2017, 127). As stated previously, oral contraceptives suppress the natural fluctuations of hormones; the result is dysregulation of fear and stress response mechanisms. It has been demonstrated that oral contraceptive pill use decreases the reactivity of the hypothalamus-pituitary-adrenal axis, which typically acts, by various direct interactions and feedback mechanisms, as a natural stress response system (Montoya, 2017, 128). Fluctuations of ovarian hormones throughout the menstrual cycle are important in the regulation of these emotional responses. These fluctuations are lacking in women who take the combination pill. Surprisingly, the same lack of hormone fluctuation is what researchers believe causes severe depression in some women (Montoya, 2017, 129). This knowledge provides a neuroendocrine link between oral contraceptives and the risk of depression. Ovarian hormone modulation of reward processing in the brain is also suppressed. This suppression could play a role in depressive symptoms (Montoya, 2017, 129). It is important to realize that not all women will experience oral contraceptive-linked depression, indicating multiple factors at play.

The suppression of estrogen and progesterone also seems to play a role in partner preference. Normal hormonal fluctuations play a role in reward sensitivity, which is important for “initiating social interaction, and allows for shifts in partner preference, satisfaction, and sex drive throughout the cycle” (Montoya, 2017, 131). The absence of these fluctuations leads to altered partner preferences along with blunted physiological responses to sexual stimuli in women who were studied. This could help explain the neurological facet of decreased libido in women who take the pill (Montoya, 2017, 131). Many questions regarding ovarian modulation of social and emotional responses and brain function are still unanswered, and this field has

received very little attention, even though the pill significantly impacts these emotional responses in some women (Montoya, 2017, 132-3).

The effect of combined oral contraceptives ranges beyond the brain and emotional responses. Oral contraception seems to have a potential impact on central corneal thickness in young women, according to Bengi Kurtul and his colleagues at Children's Health and Diseases Training and Research Hospital. Central corneal thickness values were found to be higher in young women who used oral contraceptives and researchers concluded that sex hormones "influence structural and functional aspects of the anterior and posterior segments of the eye" (Kurtul, 2016, 666). Central corneal thickness is critical in the diagnosis and treatment of several ocular conditions including glaucoma (Kurtul, 2016, 665). Several other studies have indicated "the occurrence of a variety of eye disorders in women using oral contraceptives" (Kurtul, 2016, 665). Kurtul and his colleagues proposed that central corneal thickening caused by the oral contraceptives could potentially be one cause of these reported ocular disorders, though there are likely many factors that contribute to an increased risk of ocular disease. In a normal cycling female, central corneal thickness increases during ovulation and at the end of the cycle and decreases at the very beginning of the cycle, with fluctuations in between. Because combined oral contraceptive use prevents hormone fluctuations from occurring it could cause central corneal thickening without thinning in women using the pill. It is still unclear as to exactly how the ovarian hormones affect corneal thickness, but there are both estrogen and progesterone receptors on the cornea, pointing to a possible explanation for the effects of exogenous hormones, in the form of the pill, and endogenous hormones, released from the body, on central corneal thickening (Kurtul, 2016, 667).

In a review of the impact of combined oral contraceptives on ocular tissue conducted by Moschos and Nitoda, combined oral contraceptive pill use was shown to lead to an increased risk for “dry eye symptoms, corneal edema, lens opacities, retina neuro-ophthalmologic or vascular complications” in young women (2017, 1604). Estrogen released from the pill has been linked to decreased production from and a decrease in the size of sebaceous glands, resulting in alterations of mucus secretions in the eye (Moschos, 2017, 1605). Mucus secretion is important for keeping the eyes lubricated and in a healthy state. In this review, researchers also linked the combined oral contraceptive pill, specifically estrogen, with altered corneal thickening when compared to nonusers (Moschos, 2017, 1605). Due to the number of estrogen receptors found in the eye, they proposed that eliminating the estrogen dose from the pill would effectively eliminate these issues and further risks (Moschos, 2017, 1604).

Neuro-ophthalmologic complications which could result from combined oral contraceptive use include 6th cranial nerve dysfunction, leading to decreased contraction of the eye muscles and therefore altered eye movement, damage to the parietal lobe of the brain, decreased vision, and in some severe cases total blindness (Moschos, 2017, 1607). Additional complications such as retinal artery and vein occlusions, intraocular hemorrhage, aneurysms, and thrombosis of the cerebral vessels have also been described (Moschos, 2017, 1607). These “consequences may be temporary or permanent” and may be especially likely if other risk factors are present, including diabetes mellitus (Moschos, 2017, 1607).

Research to assess the effects of combined oral contraception use on cardiometabolic risk factors, specifically in women with high testosterone levels, has shown that oral contraceptive use is linked to an increased risk for vascular disease in young women (Krysiak, 2017, 45).

Vascular disease encompasses a wide variety of disorders, which may increase one's risk for more serious complications.

One possible mechanism for explaining the risk for vascular disease is combined oral contraceptive induced endothelial dysfunction. The endothelium is the internal lining found in all blood vessels. Ethinyl estradiol is a synthetic estrogen commonly found in the combined oral contraceptive pill, which works to regulate vaginal bleeding and inhibit follicle development by inhibiting pituitary secretion of follicle stimulating hormone. It is also one of the specific types of estrogen that has been found to have an adverse effect on the function of the endothelial cells lining blood vessels. (Kluft, 2016, 145). Estrogens “induce significant changes in the coagulation (clotting) system, causing an increase in thrombin activity and in clotting factors, as well as a reduction of natural coagulation inhibitors”, which ultimately leads to increased blood clot formation and decreased clot breakdown (Lima, 2017, 648). Combined oral contraceptive use has also been found to modify “prothrombin time, activated partial thromboplastin time, fibrinogen, and D-dimers”, all of which influence the formation of a blood clot (Lima, 2017, 1605). Endothelial dysfunction may also be related to “altered levels of nitric oxide, homocysteine, and angiotensin”, particularly in women who smoke (Medeiros, 2017, 95).

Secondary to endothelial dysfunction and the increased risk of blood clot (thrombus), the overall risk for ischemic stroke, myocardial infarction (more commonly known as a heart attack), pulmonary embolism (a blood clot in the lungs), and venous thromboembolism also appear to be increased in women who use the combination pill (Kluft, 2016, 145). Much of the research indicates that this increased risk is dose-related with higher estrogen dosages, particularly 30-40 μ g, directly correlated with a significantly increased risk. Risk is also dependent on the type of progestogen contained in the pill (Weill, 2016, 4). Third generation progestogens, like

desogestrel and gestodene, have been associated with a significantly greater risk, particularly for pulmonary embolism, when compared with second generation progestogens like levonorgestrel (Weill, 2016, 4). Pills containing 20 μ g estrogen and levonorgestrel have been “associated with a statistically lower risk of pulmonary embolism, ischemic stroke, and myocardial infarction” when compared to levonorgestrel, or any other progestogen, in combination with 30-40 μ g of estrogen (Weill, 2016, 4).

Duration of use was not shown to significantly increase the risk of venous thromboembolism, and multiple studies have shown that the risk of venous thromboembolism, which increases during the initial phase of oral contraceptive use, decreases with the duration of use (Weill, 2016, 7 and Moschos, 2017, 1605). In a cohort study, Weill and his colleagues also found that duration of oral contraceptive use does not have a significant “impact on the risk of myocardial infarction and ischemic stroke” (Weill, 2016, 8). In an integrative review of current research, another team of researchers also concluded that there is “no greater risk [for these events] according to duration of use” but current users appear to be at a greater risk compared with those who no longer use or have never used oral contraceptives (Lima, 2016, 651).

Many other studies have been conducted to assess the risk of more serious complications and the role that combined oral contraceptives may play. Much of the research indicates that oral contraceptive use presents an “increased risk of fatal and nonfatal cardiovascular events”, but many other factors may play a role as well (Medeiros, 2017, 95). In discussing this increased risk it is important to remember that in a healthy individual the increase in risk is likely very low (Lidegaard, 2012, 2257). Other common risk factors for such cardiovascular events include, but are not limited to, alcohol abuse, smoking, obesity, high blood pressure, high cholesterol, socioeconomic status, sedentary lifestyle, and previous family and personal history of such

events (Lima, 2016, 651). However that being said, it is important that a physician assess each patient individually and examine her medical history in order “to determine the most appropriate contraceptive method” (Weill, 2016, 8).

It has also been determined that there is an association between exogenous and endogenous sex hormones and the development of asthma (Guthikonda, 2014, 17). Asthma is a “multifactorial disease that is influenced by the interplay between genetics and environmental factors”. In fact, the prevalence of asthma increases significantly after females go through puberty, which indicates some relationship between estrogen and progesterone and the risk of asthma. The knowledge of this relationship is confirmed by the fact that lung function varies throughout the menstrual cycle, with the fluctuations in function directly correlating with the fluctuations of hormones during the normal menstrual cycle (Guthikonda, 2014, 18). Despite these facts, the exact mechanism of how these hormones increase asthma risk is unknown. Estrogen and progesterone decrease the contractility of smooth muscle in the lungs, which would make it easier to breathe and thus, the risk of asthma would be reduced in oral contraceptive pill users (Guthikonda, 2014, 18). However, as with everything in the human body, medications do not directly target any one organ or pathway, but instead have many different effects throughout the entire body. Researchers suspect that the correlation between asthma and combined oral contraceptive pill hormones is most likely “driven by the effects [of these hormones] on the immune system” (Guthikonda, 2014, 18).

Factors such as allergens, irritants, and infection can trigger an immune response leading to asthma or asthma-like symptoms. Genetic factors can also play a role. One genetic factor that may affect the risk of asthma and asthma-like symptoms after puberty is increased DNA methylation of the GATA-3 gene. Findings indicate that combined oral contraceptive pill use

may increase methylation levels of the GATA-3 gene (Guthikonda, 2014, 24). GATA-3 is a regulator of T-cell differentiation and endocrine responses (Guthikonda, 2014, 24). Methylation of the gene decreases expression of the gene leading to negative impacts, including altered cytokine production (Guthikonda, 2014, 24). The effects of altered expression of this gene could cause asthma symptoms.

Research to determine the exact relationship, or mechanism, of combined oral contraceptive use and asthma symptoms is still ongoing. Several studies have found there to be no significant increase in risk, a decrease in risk, and even no effect at all on the risk of asthma in combined oral contraceptive users. Other research suggests that early menarche may also play a role due to longer exposure to sex hormones (Guthikonda, 2014, 18).

Combined oral contraceptive pill use has also been linked with decreased bone mineral density in adolescent females. Biazon and his colleagues found that adolescent combined oral contraceptive users “exhibited lower bone mass acquisition in the lumbar spine region and subtotal whole body” when compared to adolescent nonusers (Biazon, 2015, 18). This is likely due to the actions of oral contraceptives on the levels of estrogen in the body (Biazon, 2015, 16). Estrogen has been called the “key regulator of bone metabolism” and is known to play a role in bone mass acquisition by reducing osteoclast formation, thereby reducing bone reabsorption/breakdown, and increasing osteoblast formation, which stimulates bone formation (Biazon, 2015, 17-8 and Dombrowski, 2017, 23). This process of bone mass acquisition occurs all throughout childhood and adolescence, and as a result, adolescent girls typically have elevated estrogen levels (Biazon, 2015, 16). However, the use of hormonal contraceptives “alters the physiology” of several endocrine glands, including the hypothalamus, pituitary gland, and ovaries (Biazon, 2015, 15-6). These alterations consequently affect estrogen levels and

fluctuations, which may interfere with bone mass acquisition by altering osteoclast and osteoblast formation (Biaison, 2015, 15-6). The effects may be especially detrimental during such a critical time of development and could have greater effects on the individual later in life, including the early onset of osteopenia and osteoporosis, as well as an overall increased risk for bone fracture (Biaison, 2015, 18).

Osteoporosis and osteopenia are two diseases related to decreased bone density, which typically present later in life and are very common in females. Research suggests that onset of these diseases can be significantly delayed by adequate bone accretion during adolescence (Biaison, 2015, 18). Since the combination pill “has been shown to have a negative impact on peak bone mass development in adolescent girls”, it is predicted that oral contraceptive use may be associated with an increased risk for the early onset of osteoporosis and osteopenia (Dombrowski, 2017, 2350).

This relationship between oral contraceptive use and decreased bone mass does not appear to hold true in young women, premenopausal women, and postmenopausal women. Several studies indicate the opposite is true in that combination oral contraceptive use may “promote bone mass acquisition” in these women (Allali, 2009 & Biaison, 2015).

In a retrospective study conducted by Dombrowski and his colleagues, it was concluded that the relationship between estrogen intake and bone health was age-dependent. Young, premenopausal, and postmenopausal women without bone fractures were significantly more likely to have used oral contraceptives (2017, 2). The significance of their findings was greatest in women between 18-35 years old, but the data collected from older age groups also indicates the benefit of estrogen (Dombrowski, 2017, 4-5). It is important to note that this type of study, method of information retrieval, and the conclusions that can be drawn are limited. Several

factors including activity level and history of smoking, which may affect bone mass and therefore risk of fracture, could not be taken into account (Dombrowski, 2017, 2351). Their findings suggest only likelihood, not a cause-and-effect relationship.

Bone mass acquisition depends on many factors and level of acquisition varies among all individuals (Biaison, 2015, 15). Factors that may alter bone mass acquisition include genetics, smoking, alcohol abuse, bone density disorders, epilepsy, diabetes, anorexia nervosa, and the activity level of the individual. Some of these risk factors for decreased bone mass are also risk factors for the onset of other complications that have been associated with combined oral contraceptive use. There is very little to no evidence on the effect of progestogen on bone mass acquisition.

Though findings have been inconsistent, there is some evidence suggesting that combined oral contraceptive use may also have a significant impact on the risk of developing breast cancer. Other research states that the increased risk is small and insignificant (Hemminki, 2002, 10). Several researchers have suggested that family history, number of pregnancies, duration of breastfeeding, age at menarche, alcohol consumption, body mass index, and age when the individual started using combined oral contraceptives may influence one's risk, making the exact effect of combined oral contraceptive use unclear (Ellingjord-Dale, 2017, 10 and Ma, 2006, 43). There is also a significant amount of evidence suggesting that the presence of the BRCA1 or BRCA2 mutation in combined oral contraceptive users significantly increases that individual's risk for breast cancer (Marchbanks, 2002, 2030). Evidence suggesting an increased risk associated with duration of use has also been conflicting. White and his colleagues state that increased duration of use may lead to a small increase in risk, but findings of research conducted

by Marchbanks and her colleagues suggest duration of use has no effect (White, 1994, 505 and Marchbanks, 2002, 2026).

While overall results have been conflicting, there is “substantial evidence for the role of female hormones in the etiology of breast cancer” (Ellingjord-Dale, 2017, 11). Research suggests that estrogen and progesterone are in some way important for tumor development in the breasts (Ma, 2006, 39). However, there are several molecular subtypes of breast cancer including luminal A-like, luminal B-like, and HER2-positive, and research suggests that hormones such as estrogen and progesterone may have a different impact on the development of each type of breast cancer (Ellingjord-Dale, 2017, 11).

Other side effects of combined oral contraceptive pill use include impaired fasting glucose and insulin resistance in some patients (Medeiros, 2017, 93). These may increase the risk of developing type 2 diabetes mellitus if effects are long lasting. Use has also been shown to “lead to an increase in total cholesterol levels” in some patients, particularly those with polycystic ovarian syndrome (PCOS) (Medeiros, 2017, 98). Again, physicians must take into account a patient’s medical history including any history of dyslipidemia and diabetes mellitus prior to prescribing this medication (Medeiros, 2017, 106). More common and less severe side effects include breast tenderness, headache, and intermenstrual bleeding, known as spotting, as well as nausea, vomiting, weight gain, and mood swings (Palacio-Cardona, 2017, 840).

On the surface, most of these articles appear to have a negative message regarding contraception because of the possible risks, but they also make a point to note that their findings are not common among all individuals who use oral contraception. More research needs to be done in order to determine the exact effect of combined oral contraceptives, as many other factors play a role in the onset and continuation of the diseases mentioned here. Many

researchers have emphasized the impact a patient's medical history and lifestyle can have on the development of the above outcomes. Each doctor must take everything into account, weighing the risks and benefits, prior to making a decision on prescribing any form of contraception for a patient. It is also important that the patient be well informed of all possible risks, as well as what other factors could influence her chances of an adverse event.

The combined oral contraceptive pill can also provide various benefits and is used not only "for birth control, but also for irregular menstruation, hirsutism, polycystic ovarian disease, and dysmenorrhea", among other things (Guthikonda, 2014, 18). The use of the combination pill has been shown to reduce the "intensity and duration of menstrual bleeding" through the suppression of estrogen and progesterone fluctuations, which are involved in normal menstrual cycle. This may be especially beneficial for some women who would typically experience heavy or prolonged bleeding (Palacio-Cardona, 2017, 840). As intense, heavy bleeding is known to be one cause of anemia, combined oral contraceptive use may prove to be especially beneficial for these patients.

Hirsutism is the excessive growth of unwanted hair as the result of sex hormone imbalance. The use of oral contraceptives to regulate these hormones and keep hormones at a decreased level in these patients can have a profound impact on their physical appearance, as well as on their mental wellbeing as unwanted and excessive hair growth on the face, neck and back may be especially embarrassing for a female (Palacia-Cardona, 2017, 840).

In a cohort study performed by John Palacio-Cardona and Diana Borrero, combined oral contraceptives were found to effectively treat acne in most patients (Palacio-Cardona, 2017, 837). Acne is the "most common chronic inflammatory disease," particularly in adolescents and young women and may have a significant impact on their physical appearance, as well as their

mental state. The impact acne can have on an individual is not only related to breakouts and scars, but also low self-esteem, depression and anxiety as a result (Palacio-Cardona, 2017, 836). Results from following these women over one year indicated that continued use, specifically of pills containing 20 μ g ethinyl estradiol and dienogest, reduced inflammatory and non-inflammatory acne lesions in women of all ages and specifically those between the ages of 18-30 (Palacio-Cardona, 2017, 837). Several women in the study had a 100% reduction in comedones, papules, pustules, and overall there was a 94% reduction in acne for all women included in the study (Palacio-Cardona, 2017, 837). These acne reduction percentages are slightly higher than other studies. However, the overall consensus is that hormonal oral contraceptives can effectively treat acne in most women (Palacio-Cardona, 2017, 838). The mechanism providing this benefit is again related to hormone suppression and regulation.

Androgens are steroid hormones produced naturally by the ovaries, adrenal gland, and skin, and are known to have a role in the pathogenesis of acne vulgaris (Palacio-Cardona, 2017, 836). The most well-known androgen is testosterone. All women produce various levels of testosterone; however, some women produce more than others, or more than is necessary. It has been “suggested that there is an increased sensitivity of hormone receptors expressed by sebocytes and keratinocytes as well as increased local androgen metabolism by enzymes” in some women which could lead to acne breakouts in the individual (Palacio-Cardona, 2017, 836). Combined oral contraceptives have been shown to have an effect on endogenous “androgen production and thus positive effects on the skin of women” (Palacio-Cardona, 2017, 836). Progestogens, specifically, are known for their anti-androgenic effects and work by blocking androgen receptors in specific organs. The blocking of androgen receptors is believed to reduce not only acne lesions, but also unwanted skin spots (Palacio-Cardona, 2017, 836). The anti-

androgenic effects of hormonal contraceptives have not only proven to be effective in treating acne, but are also believed to be the reason behind combined oral contraceptive treatment of menstrual irregularity, endometriosis, hirsutism, and hair loss (Palacio-Cardona, 2017, 836).

Despite the negative effects of combined oral contraceptive use on the eye listed previously, Moschos and Nitoda cited several positive effects in their review. These include improvement of dry eye symptoms in postmenopausal women, including improvement of inflammation of the cornea and conjunctiva, prevention of cataracts, prevention of oxidative stress in the eyes, protection from degradation of corneal collagen, and treatment of age-related macular degeneration. The mechanism by which these occur was thoroughly discussed in the article, with most being linked to the vaso-dilatory and antioxidant activity of estrogens (Moschos, 2017, 1606). They also report there is no indication that combined oral contraceptives have any effect on increasing intraocular pressure (Moschos, 2017, 1605)

Combined oral contraceptive pill use has also been shown to effectively treat and manage the symptoms of polycystic ovarian syndrome (PCOS) for most women and in many cases hormonal contraceptives are prescribed as the first line therapy. The effects may be especially evident in hyperandrogenemic PCOS patients (Medeiros, 2017, 106). Despite impaired fasting glucose and insulin resistance in most PCOS patients, those who use combined oral contraceptives have been found to present with improved insulin sensitivity (Medeiros, 2017, 93).

PCOS is “associated with menstrual disturbances, high testosterone levels, infertility issues, and obesity” (Medeiros, 2017, 94). PCOS patients are also typically at an increased risk for “dyslipidemia, dysglycemia, venous thromboembolism (VTE), cardiovascular disease (CVD), and metabolic syndrome” (Medeiros, 2017, 95). Effects may be especially evident when

other factors, including age, PCOS phenotype, and underlying diabetes mellitus, are at play (Medeiros, 2017, 94). Some of the diseases associated with PCOS are also diseases that combined oral contraceptive users have been shown to be at an increased risk for developing. However, according to a review conducted by Sebastião Medeiros, combined oral contraceptives actually provide PCOS patients with improvement of and decreased risk for the development of these diseases. PCOS patients who use combined oral contraceptives have also been shown to have increased insulin muscle sensitivity, and increased sex-hormone binding globulin (SHBG), which decreases free testosterone levels, as well as total testosterone levels, menses regulation, and protection from benign and malignant endometrial tumors (Medeiros, 2017, 96-8). The combined oral contraceptive pill does not appear to significantly impact blood pressure, BMI, and waist circumference of PCOS patients (Medeiros, 2017, 99-101).

Oral contraceptive use has also proven to provide “some degree of protection against” the development of endometrial cancer (Kaufman, 1980, 1045). In a case-control survey conducted by Kaufman and his colleagues, the data collected indicated a 50% reduction in risk in women who had used combination oral contraceptives when compared to nonusers (Kaufman, 1980, 1046). They also discovered a significant “trend of decreasing risk with increasing duration of use of combination oral contraceptives”, indicating an even greater decrease in the risk of developing endometrial cancer if a woman takes the pill for a time period greater than one year (Kaufman, 1980, 1046). Kaufman and his colleagues also concluded that this reduction in risk could “persist for up to five years” after use has ceased (Kaufman, 1980, 1045).

Combined oral contraceptive use has also proven to reduce the user’s risk of developing ovarian cancer, including one of the most common types- epithelial ovarian cancer (Stanford, 1991, 543). Research conducted by Dastranj-Tabrizi and his colleagues indicates that combined

oral contraceptive use for greater than 5 years significantly decreased the chance of cortical inclusion cysts in the ovaries, and reduced the overall risk of ovarian cancer (2016, 34-5). They predicted that suppression of ovulation and gonadotropin levels, mainly by the actions of progestogen suppressing the PAX8 pathway, prevented overgrowth of the tubal epithelium (Dastranj-Tabrizi, 2016, 33). This pathway is “expressed dominantly in the absence of progesterone” and is known to play a role in tubal metaplasia (Dastranj-Tabrizi, 2016, 34). Suppression of the pathway prevents this metaplasia and the formation of ovarian tissue overgrowth. Researchers predict that suppression of the PAX8 pathway could also affect other pathways involved in ovarian cancer development (Dastranj-Tabrizi, 2016, 35). In conclusion, altering the hormone levels and therefore decreasing the chance of changes in the nature of the tissue reduces the risk of ovarian cancer.

In another article regarding the risk of ovarian cancer, it is stated that the risk reduction is found even in with women with a BRCA mutation (Jatoi, 2015, 711). It is believed that continuous ovulation predisposes the ovarian epithelium cells to DNA damage and this damage gives rise to cancer formation. For this reason, many researchers believe that the suppression of ovulation through oral contraceptive use might lead to a decreased cancer risk (Jatoi, 2015, 711).

The risk is not completely reduced and may vary among individuals given family history and other predisposing factors. Given this knowledge, Jatoi and his colleagues set out to determine “whether oral contraceptive use prior to an ovarian cancer diagnosis is associated with better outcomes” following treatment (2015, 711-2). Their results revealed that women who used combined oral contraceptives “were more likely to have no residual disease from surgery and less likely to need platinum-based chemotherapy after surgery” (Jatoi, 2015, 714). These findings indicate that oral contraceptive use is associated with more favorable progression free

survival. Progression-free survival is defined as the length of time the patient lives with a disease after initial treatment without progression of the disease. Oral contraceptive use may also lead to an improved overall chance of survival (Jatoi, 2015, 714). These researchers reiterate that age and other factors play a role, however, and their results do not agree with some of the findings from previous studies on this topic (Jatoi, 2015, 715).

My research indicates two possible mechanisms for this decreased risk of developing cancer through oral contraceptive use. As mentioned above, cessation of ovulation decreases monthly trauma and thereby limits epithelial cell DNA mutations. Researchers suggest that the more frequent the trauma, the “more apt these cells are to develop aberrant DNA mutations” (Jatoi, 2015, 716). If this is case, then it becomes clear that suppression of ovulation, via combined oral contraceptive use, would decrease the risk of ovarian cancer. A second suggested mechanism involves the suppression of matrix metalloproteinase activity. Matrix metalloproteinase enzymes are typically responsible for the degradation of extracellular matrix proteins. This activity is known to have long-term consequences and to play a crucial role in tumor development. Oral contraceptive hormones decrease the activity of these enzymes and therefore have a beneficial effect (Jatoi, 2015, 717).

Aside from the gap in knowledge of what has been researched and the questions that remain unanswered, there also appears to be a gap between research findings and what physicians and their patients know. Vogt and Schaefer, of Charité Universitätsmedizin in Berlin, Germany, conducted a study to find out how much women truly know about oral contraceptives and its risks and benefits. This study is useful because women must be informed about potential risks and benefits in order to give their consent for a treatment or to make a decision regarding their personal healthcare. Sharing information with a patient is not only legally and morally right,

it is especially important when other options are available (Vogt, 2011, 183-4). Vogt and Schaefer found that women were mostly unable to identify what they call “non-contraceptive benefits” of oral contraceptives and that there was a large gap between their perceived knowledge and their actual knowledge (Vogt, 2011, 191). The women who participated in this study did not know nearly as much as they thought they did. They concluded that there is a “need for more contraceptive counseling” to explain things like thrombotic effects of oral contraceptives and the influence of oral contraception on things like “pelvic inflammatory disease, mood, menstrual complaints, breast diseases, libido, weight and acne” (Vogt, 2011, 192). This indicates the need for continued research, as well as physician and patient education on the risks and benefits discussed here.

Conclusions

Every medication on the market has been associated with various risks and benefits. The severity of those effects can be influenced by many other factors. Those factors include, but are not limited to, the following: family history, past medical history, and various lifestyle and environmental factors. For this reason the vast majority of research that has been conducted presents this underlying message that physicians and other health care providers should assess each patient individually before deciding whether or not the combined oral contraceptive pill is the best form of contraception for that patient.

Over the last five decades the pharmaceutical industry has made birth control safer for all women by lowering estrogen doses and developing safer progestogens. Because of these changes, the chance of the adverse events mentioned here is generally low in young, healthy women. In most of those women, the benefits likely outweigh the risks. Acne treatment,

hormonal regulation, and menstrual regulation are just a few benefits a young woman might experience. While adolescents may gain some benefit from use, age at onset of combined oral contraceptive pill use should be taken into consideration as it may have significant impacts on the structure and function of developing brains and could negatively impact bone mass acquisition, leading to the early onset of osteopenia and osteoporosis later in life.

Although the majority of women tolerate this medication well, all women should be more informed of the risks and benefits so that each individual can make the best decision with regards to her health and future. It is also important that each woman is informed about the various other factors that may influence her risk and therefore, her decision to use the combined oral contraceptive pill.

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