Health, Hormones and Contraception

First Edition

This book is to help women

understand their reproductive system and factors to consider

when they are considering hormonal contraception

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First Edition

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Forward to the 1st edition

Recently, I became a member of the Contraceptive Study Group initiated and led by Dr. William Williams M.D. He brought together a group of physicians, scientists and researchers to discuss with one another their particular expertise in some aspect of hormonal contraception. My area was breast cancer. We researched topics and had regular discussions that lasted well over a year and submitted our findings to Dr. Williams. He then submitted those findings to the Federal Drug Administration (FDA) as a Citizens Petition asking for additional "Black Box Warnings" in the package insert information given with hormonal contraceptives to patients and for the removal of Depo-Provera from the market due to increased male to female HIV transmission. This would allow both doctors who prescribe them and their patients who take them to have more information with which to make an informed choice. These petitions must be submitted via an FDA form in a very detailed and rigorously documented way that includes all of the published data concerning a drug and not only those studies which support the petitioners' recommendation. Also included is the economic impact of treatment of diseases caused by the drugs as well as their impact on the environment. The Petition was submitted May 9, 2019, accepted by the FDA, given a docket number and placed on the internet for public comment by individuals or a manufacturer. To date, 148 women or their families have commented on line.

After retiring from a 33 year surgical career, I reflected upon the breast problems I had treated in over 20,000 new patients I saw during my 23 years as a breast surgeon. I wanted to put the information I had learned in a form that both women and their doctors could use. The information presented in this book is largely based upon the data gathered by Contraceptive Study Group and data I gathered answering the questions of my patients. Every new patient I saw filled out a complete Breast History and Risk Assessment form which I reviewed with them.

When I became the leader of the breast program at Steeplechase Cancer Center for 10 years, every patient screened with mammography or treated for breast cancer filled out a similar form, over 8000 a year. What was unique was that the forms not only included if a woman had taken hormones, but also for how long, what type and when during their reproductive lives. The vast majority of women I saw had either taken them in the past or taking them in the present. The Center for Disease Control and Prevention (CDC) reports 88% of U.S. women have done so. I learned the extent to which these hormones affected breasts and also impacted a woman's whole body and psyche. It was information that was new to me. Over a 36 year period working in the same community, I had the privilege of taking care of whole families of grandmothers, mothers and daughters, sisters, friends and co-workers. I became a mother at 41 years old and saw the effects of hormones on my daughter's generation and the role they play in their lives. So this booklet is dedicated to my former patients and the Millennial Generation. I give my best answers to their most frequent questions and the medical research used to answer those questions. It is intended to be a resource for women and their doctors. I hope women can use it to make informed choices for themselves and their children. I hope doctors will become aware of the lesser known adverse reactions their patients may encounter.

Angela Lanfranchi M.D., F.A.C.S March 1, 2020

Health, Hormones and Contraception

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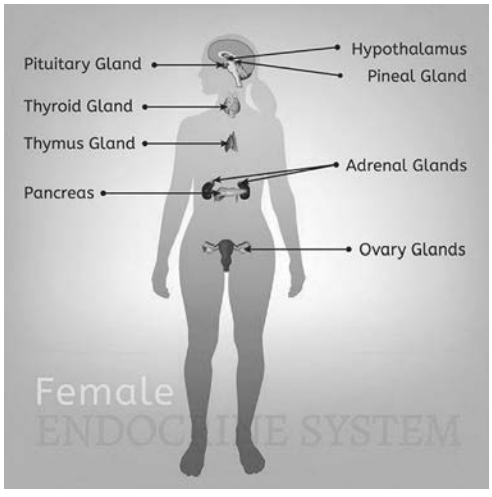
Part One

Health, Hormones and Contraception: a Woman's Menstral Cycle and Fertility

Health is defined by the World Health Organization in their constitution as a state of "complete physical, mental and social well-being and not merely the absence of disease or infirmity." The Centers for Disease Control and Prevention endorses this definition. Notice that "social well-being" is a part of health and can be defined as when we have good relationships and social stability.

Hormones can best be defined as a chemical substances produced by a gland in the body that controls and regulates the activity of other organs. Organs are parts of our bodies like our livers that perform many functions such as making cholesterol or our lungs that take out oxygen from the air we breathe so we can live. There are also "neurohormones" made by the brain or nerves that affect fertility. Hormones greatly influence our health. Simply put, they can be thought of as messengers (e.g. estrogens) made by glands, (e.g. ovaries) that go in our blood and tell other parts of our body, what to do (e.g. our breasts and uterus). Anywhere there is a receptor for this messenger to fit, like a key into a lock, there will be an effect. In the case of the female hormone estrogen, there are estrogen receptors not only in our breasts and uterus (womb) but also in our brains which affects mood and behaviors. These moods and behaviors are very apparent to parents when their child is in puberty or to husbands when their wives are going through menopause. There are receptors in many different organs that all have different purposes to keep our bodies alive and healthy. There are estrogen receptors in our skin, bones, livers, digestive tract or gut, immune system, white blood cells, heart and even blood vessels to which women with hot flashes can attest. Wherever there are estrogen and or progesterone receptors, synthetic man-made drugs designed to mimic these hormones will also have an effect. The presence of these receptors in many of our vital organs causes cross-reaction with the receptors for other hormones as well. This is why side effects of hormonal contraceptives are so varied and affect so many parts of our bodies. These are discussed in the Question and Answer section of this book with the medical references provided in Part 3 of this book. To add even more complexity, there are also 2 types of estrogen receptors, alpha and beta, with different functions that can be in the same organ. The hormone's effect is due to the balance of stimulation of the 2 receptors.

Hormones are also very powerful. The natural female sex hormone, estrogen, is so powerful it is measured in parts per trillion in our blood. It is regulated very precisely. It is made not only in the ovaries but also by our fat, liver, breasts and the adrenal glands.



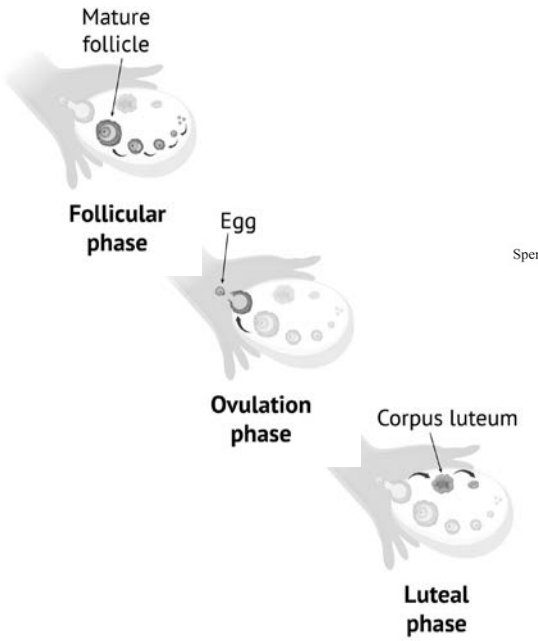
Synthetic (man-made) estrogens in hormonal contraceptives are so powerful that when excreted in women's urine collected at sewage treatment plants, the effluent discharge in large flowing rivers affects the fish downstream. The fish become infertile and develop abnormal reproductive organs. This has become a great ecological problem still not solved. These ecologic impacts from hormonal contraceptives are described in the FDA Petition on page 56-57.

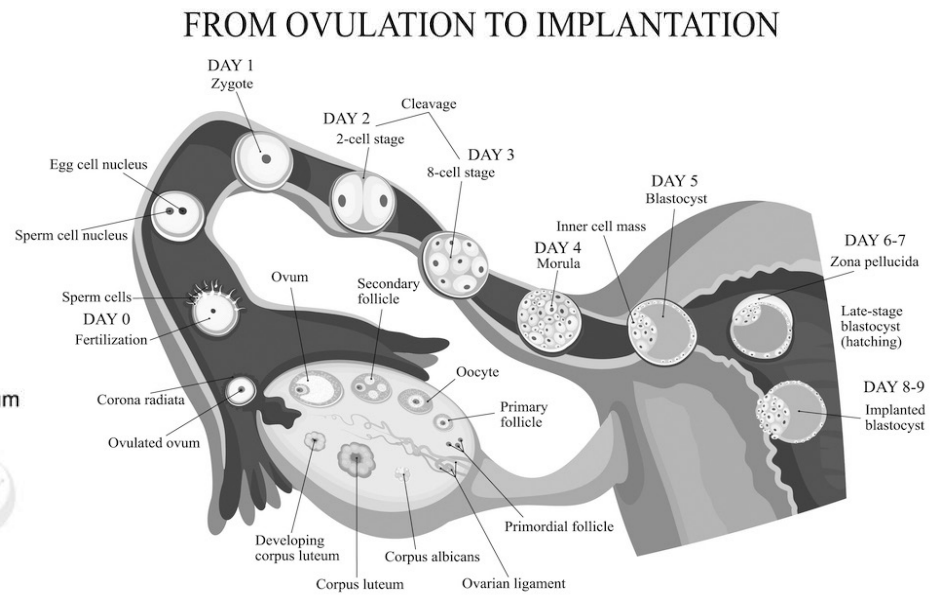
Hormones have a very complex regulation system, called the endocrine system. More than one hormone from two completely different glands might be needed to be available for one of them to have an effect. For instance, the hormone primarily responsible for breast milk production, prolactin, must have the following hormones present as well so a woman can breast feed: insulin from the pancreas, cortisol from the adrenal gland, growth hormone from the pituitary gland and thyroxine from the thyroid gland. Oxytocin, produced by nerves in the hypothalamus, is also necessary to release the milk from the breast with sucking. This means all of those glands need to be working as well.

This regulation system, the endocrine system, is like a great symphonic orchestra with many instruments but not led by just one conductor. It is a great challenge for the instruments to produce a harmonious symphony (our health), whilst all the instruments (glands) and sounds they make (hormones) affect each other. The symphony is sensitive to many influences which are usually not under our control. You can only imagine what would happen if some instruments got out of tune, stopped playing, played randomly or as happens in the case of some synthetic hormones, overwhelm with strength and loudness all the other instruments.

The Menstrual Cycle

The situation gets even more complex. There are several steps needed to produce hormones. In the case of estrogen, the brain's hypothalamus produces neurohormones (hormones from nerve tissue) which then affect another gland, the pituitary. The pituitary responds and releases its own hormones, including FSH (Follicle Stimulating Hormone) and LH (Luteinizing Hormone) which affects the ovary. At puberty the ovary has 500,000 primitive follicles containing eggs. In a healthy woman of reproductive age, every month FSH stimulates the follicle to develop and produce estrogen, which thickens the lining of the uterus in preparation should conception occur. LH then triggers the follicle, which appears like a bubble on the surface of the ovary, to release the egg. At this time, the woman is fertile. There is evidence in medical literature that men can perceive this fertility. There have been many studies in the field of evolutionary psychology supporting this. For instance, a well publicized study of lap dancers showed that they received their highest tips when in their fertile state. [Reference 1] After release, the follicle remnant (now called a corpus luteum) produces progesterone, which also prepares the uterine lining to receive the fertilized egg (embryo).





If the egg is fertilized by sperm, forming a one cell zygote (embryo) at conception, in 5 or 6 days it will become a blastocyst ready to implant itself into a uterus. Embryos at different stages are transferred into women during in-vitro fertilization (IVF) procedures at 3 or 5 days. The uterine lining was already prepared, not only by ovarian estrogen and progesterone, but also by, hCG (human Chorionic Gonadotropin). HCG is made by the embryo even before implantation. HCG is the hormone detected in home and laboratory pregnancy tests. HCG causes the mother's ovaries to produce even more estrogen and progesterone than in a normal menstrual cycle in order to support the continuation of the pregnancy. In this way, the embryo protects itself with hCG so that it can continue to grow and implant into the mother's womb.

HCG also stimulates her ovaries to produce inhibin. In this way the embryo protects the mother! Inhibin is a protein which suppresses the formation of cancer cells that can form when the mother's breasts and reproductive organs are rapidly growing in size. In fact, studies have shown injecting hCG into a breast with a cancer already formed can cause the cancer to shrink. Inhibin is also probably responsible for the fact that women who suffer breast cancer while pregnant

have the longest survival if they are able to keep their pregnancy and give birth while being treated for their cancer. [Reference 2] They can even safely receive chemotherapy in the 2nd trimester and give birth to a healthy baby.

HPL, human Placental Lactogen, produced by the placenta during pregnancy, protects both the newborn and the mother. HPL causes the maturation and development of breast tissue so that milk production is possible to feed the newborn. It also protects the mother if hPL reaches a sufficient level at 32 weeks gestation by maturing and making most of her breast tissue cancer resistant and lowering her lifetime risk of breast cancer. [Reference 3]

If conception does not occur, the uterine lining is shed in menstruation. Due to the complexity of the hormonal changes that occur during puberty in order to develop a normal menstrual cycle, teenagers will often have irregular periods. These irregular periods, which may last for years before they become completely regular, will benefit teens by lowering their breast cancer risk. [Reference 4]

Women who take hormonal contraceptives have withdrawal bleeding, i.e. the uterine lining sheds when the hormones in their contraceptives are stopped. They no longer have normal menstrual cycles with cyclic changes in fertility. Pharmaceutical manufacturers have found that women prefer "regular periods" and provide them using the "dummy" pills without hormones in the pill packs. For instance, women on the Pill shed their uterine lining and bleed while they are taking a week of pills without any hormones in them due to hormone withdrawal.

Therefore it is a mistake to believe that hormonal contraceptives "normalize" or correct irregular or abnormal menstrual cycles. More accurately, they end the natural menstrual cycles of the woman and replace them with withdrawal bleeding.

Other women with contraceptives that constantly release hormones like the Mirena IUD or Nexplanon implant or Depo-Provera injection will often have irregular bleeding. Some contraceptives like Seasonique pills produce no menstrual bleeding for months.

Summary:

Health is not just an absence of disease that needs treatment with drugs. Health is a feeling of well-being. It involves physical, mental and social well-being. Hormones made naturally by our glands are potent and impactful affecting many and not just a single organ. Complex sequences of brain and ovarian hormone secretion are needed for a regular menstrual cycle. Hormones made by the embryo soon after conception also impact a woman's hormonal state. Controlled by the endocrine system, the production and regulation of hormones in the body is very complex. The introduction of synthetic hormones for contraception increases the complexity. Inadvertent problems can be caused in the many organs in the body that have estrogen and progesterone receptors. Hormones made by the embryo/fetus and placenta during pregnancy result in the maturation of breast tissue and lifetime breast cancer risk reduction for the mother.

Contraception can be defined as the deliberate prevention of conception by any of various drugs, techniques, or devices. It is also commonly referred to as birth control and commonly means the avoidance of pregnancy. Contraception is derived from two words; 1) contra: against and 2) conception: which is the initiation of life beginning when sperm and egg unite to form a one cell zygote or embryo as it is defined according medical embryology texts.

Contraception is also sometimes thought of fertility control and family planning. Some methods of fertility control, fertility awareness methods or natural family planning, can also be used to naturally enhance the chance of achieving pregnancy. **During a menstrual cycle, women are fertile only about 4 days or about 100 hours a month.** When a woman desires to control her fertility so that she only gets pregnant from sexual intercourse when she wants a child, she commonly seeks what are known as methods of contraception. It is important for her to be aware of what those words mean both medically and in common parlance so she can make choices that are best for her health.

For example, hormonal contraceptives biochemically act as abortifacients, i.e. causing abortions by preventing an embryo from implanting into the wall of the uterus. These changes are documented in the Wilks article on page 67. Despite these biochemical changes, approximately 9% of women on the Pill will still get pregnant every year. The CDC document "Effectiveness of Family Planning Methods" which details the failure rates of different hormonal contraceptives is on page 76.

According to the most recent governmental statistics available in 2019, there are 61 million US women of reproductive age, i.e. ages 15-44 years old. Of these women, 15.9% use the Pill. Therefore, as there are 9,699,000 women on the Pill which has a failure rate of 9%, 872,910 women a year will have an "unplanned pregnancy". About 58% of those women will give birth and about 42% (or 366,622 women) will have abortions according the Guttmacher Institute [Reference 5].

Some women also consider induced abortion as a method birth control and family planning. There are nations and cultures such as the countries of the former USSR which historically chose induced abortion as their primary method of birth control. About half of the women in the U.S. who choose abortion to end a pregnancy will have more than one.

Therefore, when a woman chooses what are commonly referred to as "contraceptives", they may include drugs or devices which act as abortifacients, i.e. causing embryo loss after conception has already occurred while taking the contraceptives, such as IUDs or hormonal contraceptives. This is very important information to those in some religious groups or those who have other objections to abortion. The term "complete reproductive control" usually means a method of fertility control to prevent conception with induced abortion to be used when a chosen method fails.

Summary:

Each woman is a unique individual in a particular culture or social setting. It is important for her to understand the meaning of terms when choosing a method of fertility control that is consistent with her beliefs and culture. It important for her to understand the way her chosen fertility control works in her body and the likelihood of conception before she makes a choice. This will avoid negative emotions that can occur should she learn of them subsequent to her choice or if she finds herself in a dilemma of an unplanned pregnancy.

Part Two

Common Questions

What should I do before deciding whether to use a hormonal contraceptive?

A woman should see her doctor for a complete history and physical before deciding whether to use a hormonal contraceptive as there are many things to consider before an informed choice can be made. No book can fully inform you. They can make generalizations that might apply to you but each woman is unique physically, mentally and socially. You will only be fully informed when you get to ask questions of a healthcare provider knowledgeable about the hormonal contraceptive drugs that they prescribe. That is why this book also has the information your provider can readily understand such as the FDA petition with results of the latest studies concerning the side effects or adverse reactions a woman might encounter taking hormonal contraceptives in medical jargon which is difficult for many people not working in a medical field to understand. Since doctors can't always be aware of everything or know everything, (even though we want to or think we do), you might want to show the references and studies upon which this book is based which concern one of the side effects that you may be particularly worried about in your specific circumstance. According to the American Academy of Family Practice, about 65% of women who start hormonal contraceptives will stop them due to side effects [Reference 6]

A complete medical history should always be done before a woman chooses the best method of family planning for her unique situation. For instance, if she has had a history of breast cancer, she should not take hormonal contraceptives that could increase her risk of cancer reoccurrence or a new one being formed. If she has hypertension, smokes, has diabetes or high cholesterol her risk of a heart attack multiplies by 5, 12, 16 and 23 times respectively. The risk of life threatening pulmonary embolism is tripled while on the Pill. Each year in my New Jersey hospital I would see 2 or 3 young women who died from an embolism. The last had driven her car for 5 hours straight to get home for Christmas break. My first was a college friend who had injured herself after falling off a horse. While the risks or chance that they happen are low they are real. There are 12 million women taking these drugs, so even low risks cause tens of thousands women to be impacted.

A family medical history should always be taken when choosing a family planning method. For instance, if a woman has a family history with several members suffering from leg blood clots, she is probably not a good candidate for hormonal contraception that contains synthetic estrogen. She may have inherited a clotting disorder such as Leiden's syndrome which makes her too high a risk for developing life threatening blood clots. Other hereditary conditions causing clotting are deficiencies in protein C & S and antithrombin III.

A psychiatric history should also be included. All forms and methods of delivery of hormonal contraception have been shown to be associated with depression and increased suicide rates after just 2 months of use. A large 2017 Danish study published in the American Journal of Psychiatry of a nearly half a million women who had no previous mental health issues, e.g. psychiatric diagnosis or use of antidepressants, were studied. Compared with women who never used hormonal contraceptives, there was a 97% increase in suicide attempts and 208% increase in suicides. Suicide attempts were greatest for the patch, with a 228% increase. Even the "mini-pill" had a 158% increase in risk. [Reference 7]

A physical exam should also be done before deciding whether to use hormonal contraception. For example, a doctor may find a lump in the breast or find an abnormal Pap smear which needs evaluation. Combination hormonal contraceptives are considered carcinogens for breast, cervical and liver cancer by the International Agency for Research on Cancer, a part of the World Health Organization. This publication can be downloaded at:

https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Combined-Estrogen--Progestogen-Contraceptives-And-Combined-Estrogen-Progestogen-Menopausal-Therapy-2007

Social, cultural or religious factors may also exclude some forms of fertility control while other forms can be embraced. Some women have social or religious objections to abortion. An embryo is the term used for human life in the womb up to 2 months. Hormonal contraception is known to interrupt the life of the early embryo by preventing implantation. After 2 months in the womb, the embryo is spoken of as a fetus, derived from the Latin for "little one". Also, the woman who relies solely on hormonal contraception taken as directed on the label may still get pregnant as discussed below.

A woman should also know how long she is planning on using hormonal contraceptives. All drugs have risks but risks increase with the length of time that a risk is taken. For example, smoking a pack of cigarettes a day for one year does not appreciably increase lung cancer risk. Smoking for 10 years does. Unfortunately, due to cigarettes addictive nature, most people who start smoking continue for many years, increasing their risk greatly.

Teenagers who start the Pill during puberty for acne or irregular painful periods will often continue because they become sexually active and then continue until they marry and then continue until they achieve financial stability before their first child. Ten, twenty and even thirty years may go by while a woman is taking the Pill resulting in higher risk of side effects some of which life are threatening. At least 20 percent of American women remain childless either by choice or fertility problems. They may only become aware they are infertile when stopping the Pill and finding they have difficulty getting pregnant.

How well do hormonal contraceptives work in preventing pregnancy?

It is important to know first how well a drug will work to prevent pregnancy when a woman chooses a method of contraception. There is presently no hormonal contraceptive available that prevents pregnancy 100% of the time if a woman has intercourse. According to the CDC (Center for Disease Control) 9% of women using the Pill, patch or ring will get pregnant the first year they use these methods. As there are presently over 9 million women taking the Pill, 872,910 women a year will have an unplanned pregnancy the first year while taking the Pill. About 58% of those women will give birth and about 42% (or 366,622 women) will have an abortion. Another 3 million women take other types of hormonal contraception such as "the minipill", a progestin only drug. The minipill has an even higher failure rate of 13% and must be taken at the same time every day to be effective. The minipill allows ovulation to occur in about 40-50% of cycles. Injectable progestin, such as Depo-Provera, has a 6% failure rate and requires an injection every 3 months. The CDC chart of "Effectiveness of Family Planning Methods" of typical use of all contraceptive methods on page 76.
Most women taking hormonal contraceptives believe they are 100% effective if they take them as directed on the package. Sometimes a woman will never miss a Pill, but another drug she is prescribed will make the Pill ineffective. Even if hormonal contraceptives are taken in a way where pills can't be missed like with the Mirena IUD or the Depo-Provera injection, an "unplanned pregnancy" may occur especially in very young women because they are the most fertile. An IUD or intrauterine device containing a hormone, can prevent an embryo from implanting should conception occur, yet they still have a very small failure rate of up to 0.8%.

About 85% of fertile young women will get pregnant over a year's time if she has intercourse without using any form of contraception. Women should know the failure rate of their birth control because if for social, cultural or religious reasons they are opposed to abortion, a pregnancy may present a dilemma or major challenge they would rather not face. Typical use is the way women who follow the instructions with their prescription normally take them.

Will birth defects be caused if I get pregnant while taking oral contraceptives?

A large 2016 study from Denmark showed no increase in major birth defects. Many studies have been done over the past decades. [Reference 8]

Are there any pregnancy related problems if I get pregnant while taking oral contraceptives?

There is some evidence that the pregnancy may be associated with an early (preterm) birth of the newborn and/or the newborn being smaller than normal (low birth weight) the closer the dose is to conception. [Reference 9]

What drugs are in hormonal contraceptives?

Drugs used for contraception contain synthetic female hormone-like drugs which are chemically classified as sex steroids. As described earlier, hormones are naturally occurring substances made by glands that act as messengers to many organs in our bodies. They are very powerful in terms of their potency and effects. Hormones can affect each other's functions and are part of a delicately balanced endocrine system. In a natural healthy state, the female hormones estrogen and progesterone last only a short time in the body after they are made so their effects are limited. In order to be effective for contraception, natural estrogen and progesterone must be changed to synthetic drug forms that will stimulate estrogen and progesterone receptors. They must last longer in the body in order to have the desired effect of preventing conception. They must also be resistant to biodegradation so that when taken orally and are circulated first through the liver, they are not broken down through liver metabolism to form inactive metabolites. This increase in continued potency allows only one pill to be taken once a day.

Hormonal contraceptives require estrogen-like and progesterone-like steroidal drugs such as ethinyl-estradiol and/or a progestin, to be used. There are many synthetic progestins and each type has their particular effect. For example, "third generation" progestins were created to decrease the Pill's association with heart attack and stroke, however they were found to increase a user's risk of leg blood clots that can be life threatening if they go to the lung, called pulmonary embolisms or venous thromboembolisms.

The synthetic estrogen-like drugs and progestins can be used in combination contraceptives as estrogen-progestin combination drugs (COCs) or alone as progestin only contraceptives (POCs). POCs are also referred to as progestin only pills (POPs) in medical literature. In our FDA Petition they are referred to as POCs, so I will use the POC acronym.

The first commercially available birth control pill 60 years ago in 1960 was a high dose combination synthetic estrogen-progestin drug, a COC, Enovid. Although studies showed the carcinogenic effects of these drugs by the 1970s, it was thought that the small elevation in breast cancer risk was due to other factors such as better screening tests. However, evidence continued to mount with increases in breast cancer risk from 1974 through 1986, so that by 1991 the National Academy of Sciences (NAS) issued a report acknowledging the increase in breast cancer in young women but attributed the risk to delay in childbearing by oral contraceptives. They felt more studies were needed before concluding that oral contraceptives were carcinogenic. However, since 2005, all COCs have now been recognized by the World Health Organization as causing breast, cervical and liver cancer. In common parlance, oral contraceptives are spoken of as "the Pill" and refer to combination synthetic estrogen and progestin drugs. The "minipill" is a low dose progestin only drug. There are also injectable and implantable progestin only contraceptives.

How are hormonal contraceptives delivered into a woman's body?

The Pill, a combination oral contraceptive drug, is taken by mouth. Because they are "eaten" they go into the digestive system or gut first. From there they are transported to the liver before reaching the heart from where they can be circulated to the brain, ovaries and uterus for their desired effect of making a woman infertile. They must not be greatly metabolized or changed or by the liver otherwise they would lose effectiveness. As the drugs have more potent effects than natural hormones in a normal menstrual cycle, they create a "pseudo-pregnancy" state, i.e. the body thinks it's already pregnant so does not release an egg. However, despite these very powerful synthetic drugs, women will sometimes still produce an egg resulting in pregnancy if sperm are also present.

Other combination drugs can be delivered into the patient vaginally, such as the Nuva-Ring or through the skin, as "the Patch". The drugs in the Patch and Nuva Ring pass directly into the blood stream avoiding the liver. With the Patch, women achieve 60% higher levels of synthetic estrogen than the Pill which may account for the increased risk of blood clots which can cause strokes, heart attacks or leg clots with the Patch. Progestin only drugs can be implanted under the skin, Implanon, or given as an injection every three months.

What are the health benefits of hormonal contraceptives?

There are the beneficial effects on "menstrual cycles", ovulation and cancer risk. They are increased "menstrual" regularity, decreased blood loss leading to iron deficiency anemia, decreased dysmenorrhea (painful periods), decreased ovarian cysts, and decreased endometrial (uterine) and ovarian cancers.

Are there adverse side effects with hormonal contraceptive drugs?

Adverse side effects are frequent with hormonal contraceptives. A 2010 review article in the American Family Physician, the journal of the American Academy of Family Physicians stated "Adverse effects of hormonal contraceptives usually diminish to the point of acceptance with continued use of the same method. Reassurance that symptoms will likely resolve within three to five months is often the only treatment required. Despite the transient course of these effects, a population-based survey found that **64.6 % of women who discontinued oral contraceptives did so because of adverse effects.**"(emphasis added) [Reference 6]

However, in my experience, many women would not accept even "diminished" side effects if they knew they could achieve their goal of fertility control with another method. Why should a woman just accept feeling nauseous or depressed or any other adverse effect she develops? Why should women have to risk her health and well being to control her fertility when other methods without side effects are available to her? She should be made aware and informed of all her choices.

There are adverse side effects with all drugs so every woman must make a risk/benefit analysis based upon their own medical and family history, their state of health, their own feelings about how much risk they want to take and the advice of their doctor. In other words, women require a lot of information if they are to make the best choice for themselves and have informed consent. In my experience, many women are unaware that there are forms of birth control that require no hormones e.g. double barrier methods such as using a diaphragm with spermicidal jelly and a male condom together. Another hormone free method is using a Fertility Awareness Method, also previously referred to as Natural Family Planning. During the short fertile time each month, a woman can use a barrier method or abstain from intercourse. While some natural family planning techniques may use only one observable sign of fertility like the quality of cervical mucus, others use two, such as cervical mucus and temperature changes. (I know there can be an "ick factor" here: mucus, ugh! However, after speaking with hundreds of patients who inquired, I could usually show them they were aware of them but didn't know what they signified. For example, after wiping dry after urination, women are aware of the occasional discharge similar to egg white, i.e. clear white and stringy. That is the slippery S-cervical mucus signifying fertility.) Others methods are more complex using measurements of hormones. Some fertility awareness methods have been scientifically tested and have found to be at least as reliable as hormonal contraceptives in postponing pregnancy. Some fertility awareness methods are listed on page 77.

These methods of fertility awareness have been shown through medical research to be effective in postponing as well as achieving conception. These methods need to be taught and practiced but have the advantage of being without continued cost and adverse side effects which are common with hormonal contraception. Women are usually unaware of these other methods and studies. However, most are aware of television commercials on TV by Big Pharma. They show the benefits of the Pill such as unblemished skin and pictures of happy, beautiful women but ironically are also accompanied by happy voiceovers saying the Pill can also cause strokes without pictures of young women in wheelchairs. One of my first patients as an intern in 1975 was a 26 year old woman hemiplegic in a wheelchair from a stroke. She had migraines, a relative contraindication for the Pill, but had taken the Pill after the birth of her daughter who was 2 when I saw her.

The information taught with fertility awareness and natural family planning methods can be learned once and then be used throughout a woman's life. There is little monetary profit for the training which could be used for marketing and promotion of these methods. It is time consuming for doctors to teach or discuss during office visits. Doctors are trained to use drugs and surgery. Pharmaceutical companies have the large budgets to give doctors in training lunches or dinners while listening to drug information or conferences at desirable venues to showcase new drugs and samples of their products.

They also have large budgets to do studies to validate their drug's effectiveness to promote its use. Thankfully, there now laws that limit the amount of gifts Big Pharma can give to doctors and doctors in training.

Why is there a wide range of adverse side effects with hormonal contraceptives?

There is a wide range of side effects of hormonal contraceptives because these synthetic steroid drugs, which mimic the structure of female hormones, attach to all of the natural estrogen and progesterone receptors a woman has throughout her body and not just the ones in her brain, ovaries and uterus for the desired contraceptive effect. As stated earlier, there are estrogen hormone receptors in many organs of a woman's body. Estrogen receptors can be found in our brain, bones, breasts, liver, digestive tract, uterus, cervix, ovaries, bladder, heart and blood vessels, immune system and skin. Any organ that has these estrogen receptors will be affected by the synthetic estrogen and/or progesterone like drugs found in combined oral contraceptives such as the Pill, ring or patch. There are also progesterone receptors in the brain, fallopian tubes, uterus, cervix and breasts.

What are the adverse side effects of hormonal contraception?

The following is a summary of adverse side effects or adverse reactions of hormonal contraception:
Acronyms used:
COC = combined estrogen-progestin contraceptive (Pill, Patch, Ring)
POC = progestin only contraceptive (Depo-Provera shot, "mini-pill", Norplant, Mirena IUD)
DMPA= Depot Medroxyprogesterone Acetate (Depo-Provera)

Major Adverse Effects

(Medical documentation for these are in FDA Petition pages 15-67.)

Increased risk of male to female HIV (AIDS virus) transmission with DMPA (Depo-Provera)

Breast Cancer

Cervical Cancer

Crohn's Disease

Ulcerative Colitis

Systemic Lupus Erythematosus

Depression, Mood Disorders, and Suicide

Multiple Sclerosis

Interstitial Cystitis (inflamed urinary bladder)

Osteoporotic Bone Fractures (highest for POCs)

Deep Vein Thrombosis (leg blood clots with COCs and POCs)

Increased Body Mass (Weight Gain) highest for POCs with decrease muscle and increase fat

Urogenital Effects with COCs : bacteria and urinary tract infection, female sexual dysfunction with dyspareunia (painful intercourse) and decreased libido (sexual desire)

Venous Thromboembolism: pulmonary embolism (blood clots in the lung) COCs and POCs

Atherosclerosis and Cardiovascular Events: Blockage of arteries with plaque causing strokes and heart attacks

Minor Adverse Effects

(Partial list, in present patient information from manufacturers)

Breast: tenderness, pain, enlargement, secretion, proliferative breast disease

Cardiovascular disease (related to blood vessels and heart): hypertension, phlebitis

Digestive tract (GI) symptoms: nausea, abdominal bloating, diarrhea, vomiting

Digestive diseases: gallbladder stones, pancreatitis, cholestatic jaundice Budd-Chiari syndrome (blockage of liver veins to vena cava) benign liver tumors, liver cancer

Gynecologic: vaginal discharge, breakthrough bleeding and inter-menstrual spotting, frequent Candida infections, post pill loss of menstrual cycles or ovulation, ectopic pregnancy

Immune function: Increase in risk of infection with HPV (human papilloma virus), erythema multiforme

Metabolic changes: hypertrigylceridemia, high cholesterol, fluid retention, edema, glucose intolerance (diabetes) low folate levels (which can cause birth defects)

Neurologic changes: headaches, dizziness, nervousness, chorea, optic neuritis, mood changes of depression and decreased libido, pseudotumor cerebri

Ocular (eye) problems: retinal thrombosis with complete or partial loss of vision, contact lens intolerance with curvature changes of the eye's lens

Skin changes: acne, hirsutism, melasma, rash, scalp hair loss, erythema nodosum

Drug interactions with increase or decrease in levels of co-administered drugs and change of efficacy of drugs

Drug interactions leading to decreased contraceptive effectiveness, increased levels of estrogen or changes in levels of other drugs being taken

Changes in laboratory tests with increased and decreased clotting factors, increased total thyroid hormone, increase in total levels of adrenal steroids and sex steroids, increase triglycerides, reduced glucose tolerance, lower folate level

Included in this book is a submitted FDA Petition which requests more accurate labeling for hormonal contraceptives.

It contains the medical literature documenting the most serious adverse side effects. The FDA petition also states whether combination estrogen-progestin drugs (COCs) or progestin only drugs (POCs) or both are associated with each of the adverse effects. Also listed are the economic impacts regarding the costs to treat these adverse effects. As men do not take hormonal contraceptives, these adverse effects were studied only in women. Men also have estrogen and other hormone receptors in their body. When developing hormonal contraception for men in the 1960s, changes in their testicles with the contraceptive drugs caused development of these drugs to cease.

What are some of the contraindications to COC hormonal contraceptives according to manufacturers?

A contraindication is a situation in which a drug should not be used due to potential harm. These include: leg blood clots or pulmonary embolism or past history of those conditions, coronary artery or brain artery disease, angina, stroke, transient ischemic attack (TIA), abnormal heart rhythms, family history clotting disorders, major surgery with immobilization, diabetes with vascular involvement, headaches with neurological symptoms, uncontrolled high blood pressure, present or history of breast cancer, cancer of the uterus lining, abnormal genital bleeding, jaundice with pregnancy or contraceptive use, benign liver tumors or liver cancer, suspected pregnancy and cigarette smoking.

Is it true that COC hormonal contraceptives are linked to breast and other cancers?

Yes, they are recognized to be a cause of breast, cervical and liver cancers by the International Agency for Research on Cancer, a part of the U.N.'s World Health Organization. The information can be found at: **https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Combined-Estrogen--Progestogen-Contraceptives-And-Combined-Estrogen-Progestogen-Menopausal-Therapy-2007**

Is it true that the increased breast cancer risk from a hormonal contraceptive returns to normal once the drug is stopped?

About ten years after a woman stops hormonal contraceptives, a woman's risk of breast cancer returns to normal. The reason is the slow growth rate of the average breast cancer cell that may have formed while she was taking the hormonal contraceptive. To grow from one cancer cell (which is not detectable) that keeps doubling until a cancer is big enough to be detected with mammography is formed takes from 8-10 years.

Is it true that the pill reduces the risk of ovarian, uterine and possibly colon cancers?

While it is true that women have a reduced risk of ovarian and uterine cancers, it is not a good "trade off". In 2020, of all women in the United States with cancer, 30% have breast cancer, 7% have uterine cancer and less than 3% have ovarian cancer. Another question is why should a woman expose herself to a carcinogen to control her fertility when other methods are available? Recent prospective studies have not shown a reduction on colon cancer.

Can oral contraceptives change our brain structure?

A recent 2019 brain MRI study of healthy women was presented at the Radiological Society of North America and gained much public attention. Researchers found that women who were taking oral contraceptives have a smaller hypothalamus than women not taking oral contraceptives. The hypothalamus is a very important part of our brain which is involved in the menstrual cycle as discussed earlier in Part One. The hypothalamus also helps regulate body temperature, mood, appetite, sex drive, sleep cycles and heart rate. This may explain the increase in depression and suicide while taking oral contraceptives, as well as decreased libido. Smaller sizes are associated with depression and more anger. There was no evidence that the oral contraceptives affected cognitive performance, our ability to think. Another 2015 study found that women on oral contraceptives had thinner brain cortex in some areas by MRI. [Reference 10]

Why should women want to know about the adverse side effects?

1. Adverse effects are more likely to be treated properly by avoiding unnecessary additional drugs.

It is well-known that some high blood pressure medications may cause symptoms of Parkinson's disease. Sometimes patients will get treated with anti-Parkinson drugs. Instead their high blood pressure treatment should be changed. These patients may then get side effects from the anti-Parkinson drugs without relief. Similarly, if a woman develops nausea or jaundice while on hormonal contraception, knowledge that her hormonal contraception may be a cause should be investigated before anti-nausea medications and lots of testing is done. Many times women do not think of hormonal contraceptives as the powerful sex steroidal drugs they are and do not list them when asked for a list of their prescribed medications.
In my practice, I had a green colored sheet which was used to ask patients to write down their medications. My pink breast history sheet would ask if they were taking hormonal contraceptives. I estimate that 30-50% of my patients listed their hormonal contraceptives on the pink sheet alone. They weren't trying to hide their use. They just did not consider them medications! The most common reason they gave when asked why they were not included on the green sheet was that the hormonal contraceptive was a "separate category".

This is an example of why it is necessary for women to identify and know their contraceptive drugs as medications with potential adverse affects. Women may have the cause of their phlebitis (leg vein bloods clots) to be unidentified so that prevention will not be undertaken. Legs blood clots are life threatening if they break and travel to the lungs, which is a pulmonary embolus. The vascular specialist treating them does not see oral contraceptives on the patient's medication list. He may overlook the cause of their phlebitis by being more concerned with proper anticoagulation treatment and an evaluation to see if a venous filter is needed to prevent a life-threatening pulmonary embolus. The specialist may concentrate solely on monitoring the progress of the therapy and preventing permanent leg swelling if the vein valves have been damaged.

2. Women may need to be screened for adverse effects.

For instance, if a woman has a history of depression, she should be made aware of the fact that her depression may increase with hormonal contraception. People who are depressed often don't think clearly. If the prescribing doctor does not check and screen her for developing symptoms she could become suicidal and successful in a suicide attempt. Maybe she would go to a lay counselor for her depression who does not make the connection. Physicians who know their patients would have to actively screen them with appropriate questions.

3. Women need informed consent when making any choice of hormonal therapy.

Women are intelligent. They know their bodies. They can consider their personal situation and know what's best for them. However, they may not be able to read all the fine print that comes with a package insert. They should be able to rely upon their doctors to guide them. However, there is often a bias within the medical profession that when the risk of an adverse event is low, it's worth taking the risk. However, when that low risk event occurs in a woman or their minor child, they often feel differently. Women often believe hormonal contraceptives are 100% effective in preventing pregnancy when they are not. Women also are not aware they are only fertile about 100 hours or 4-5 days a month. They can reliably learn to recognize those fertile days when they can abstain or use safe combined barrier methods. Unfortunately, it is often too much easier and less time consuming to prescribe a daily Pill than to instruct a woman how to reliably detect her fertile days.

4. Women need the information when guiding the choices of their minor children.

Often the Pill is seen by teenagers as a rite of passage and a responsible thing to do. In my geographic area, New Jersey, parental consent is not needed for teens over 13 years old. Sometimes the Pill or other hormonal contraceptives are

offered to their minor child without the parent's knowledge. Sometimes a parent will bring their child to a doctor because of acne, irregular periods or painful menstrual cramps. Combined contraceptives will improve acne, give regular "periods" due to the regular withdrawal of the contraceptives in dummy pills, and relieve menstrual cramps because the lining of the uterus thins and results in light periods. Sometimes both the parent and the child are grateful for the other benefit, contraception, just in case it is needed or wanted. However, these conditions of acne, irregular periods and menstrual cramps have other effective treatments without life threatening or severe adverse reactions. In fact, irregular periods are very common in teens and provide a benefit in that they reduce the risk of breast cancer. A study showed a teen with irregular periods for 5 years had a 20% reduction in breast cancer risk compared to those who cycled regularly within 1 year of their first period, menarche. [Reference 2] A minor child may not be aware of a strong family history of breast cancer and hormonal contraception would add to her already increased risk. A minor may not know that there was a family history of blood clots making her risk for blood clots with hormonal contraception even higher and potentially life threatening. If a mother is unaware that her child has had a Mirena IUD placed with the risk of pseudotumor cerebri, which is a buildup of pressure on the brain, she might not take seriously her child's complaint of headache until the more serious symptoms of vision loss develop. This is why it's so important for a parent to be with their minor child at doctor appointments. There are magazine articles and internet sites which inform children that they can go to their pediatrician for birth control and the pediatrician can write a code for the office visit that won't disclose to the parent through the insurance claim that the hormonal contraceptives were prescribed. Many pediatricians are unaware that the transmission of the HIV and HPV viruses is enhanced by hormonal contraceptives and other adverse effects. Overall, the risk of breast cancer is increased by the Pill (COCs) about 30%, not a big number for epidemiologists. However, they are largely unaware of the 2009 Dolle study which showed a 320% increase in triple negative breast cancer in women under 40 who took the Pill greater than a year. Another important concern in minors is their developing brain and evidence that oral contraceptive will make the hypothalamus smaller. This finding is too recent to know its long term consequences.

What should women know about their fertility when choosing hormonal contraception?

Women become less fertile as they age, especially after age 30. Women who choose to delay pregnancy should be aware of this fact. Recent census bureau data showed 31% of women between the age of 30-34, and about 20% of women between the ages of 40-44 were childless in 2016. Some women may choose to remain childless.

Women who become infertile while on the Pill, believing that they can have a child no matter their age, find that fertility treatments are not only expensive but are rigorous in the time and procedures they must undergo. Successful treatment is uncertain.

Women also sometimes go through an unexpected early menopause in their 30s and then find getting pregnant exceedingly difficult through reproductive technologies.

Is there ecologic damage to our environment from hormonal contraceptives?

The ecologic problems caused by hormonal contraceptives that get into our water supply are detailed on pages 56-57 of the FDA petition. There are about 13 million women using hormonal contraception. These powerful steroidal drugs get into the environment through waste water and become "endocrine disrupters ". They not only affect the aquatic organisms such as fish, but get into our environment. These disrupters have been implicated in declining fertility rates and as a cause of 50% reduction in sperm counts in human males since 1973.

Conclusion:

A woman needs to remember that fertility is not a disease. In fact, fertility is a sign of good health because it means multiple complex glands in the endocrine system are functioning normally. The control of her fertility should as effective as possible with the least adverse effects. Sometimes it is worth the future risk of cancer or even death if a drug is needed to fight a potentially lethal infection or debilitating disease. However, a woman should be the one who decides how much

risk to take once she is apprised of all the risks and the alternatives.
Learning fertility awareness or a natural family planning method of birth control is empowering for women. They learn to become sensitive to the signs that their body gives them when they are fertile for just a few days a month. They can use those signs to postpone or achieve pregnancy. Through the charting of their menstrual cycles they may discover an abnormality that can lead to early diagnosis of a developing medical condition. Although the CDC has listed them as having a failure rate of 24%, the CDC lumps all methods together. The list of methods I give you in the reference section have efficacy rates comparable to the Pill and you can get those rates on line. The methods are completely natural and do no harm to the earth's ecology and animals which have been adversely affected by synthetic hormones discharged into the rivers or used to promote growth of meat. Caution should be used even though the FDA has produced guidelines for what are determined to be residual safe levels of these hormones in consumed meat products and in the treated animals.
As a breast cancer surgeon, I developed a bias. Each individual OB-GYN who prescribes the Pill may see only one to three patients in their 30s or early 40s with breast cancer a year. Breast cancer in very young women is uncommon. He then refers his patient to a breast surgeon who sees too many. He may never see her again as after she is treated for cancer she commonly becomes infertile. She may only see her cancer specialist and medical specialist in follow up. Out of sight can be out of mind. The increased risk of breast cancer with the Pill is overall about a 30%; not very high in epidemiological terms. But I can remember each of my patients who were 20 or 30 years old when I treated them for breast cancer.

As a breast surgeon who had a busy practice, I saw far too many thirty and forty year old women with breast cancer. According to a 2011 study by Parkin in the British Medical Journal, 14.5% of all premenopausal breast cancer was attributable to hormonal contraception. In the United States that means over 8,000 young women this year get breast cancer because they took hormonal contraception.

The risk of metastatic breast cancer in women under 40 has been steadily increasing 2% per year since 1976. I saw what it did to their lives and their children, especially when they were single mothers with toddlers. I saw what it did to their husbands, significant others, family members and co-workers. Like a pebble thrown into a pond, there were ever widening circles of lives affected by that one woman's cancer. I also treated many women with painful breasts and proliferative breast disease brought on by the Pill who didn't know there were other ways to control fertility besides hormonal contraceptives or a condom.

When I was young and fertile, I didn't know about all the methods available to me for family planning. I didn't know much about the complexity of a menstrual cycle even though I was biology major with a good GPA. Even when I was in medical school I didn't know the risk for adverse reactions with oral contraceptives. My hope is that with this book women will empower themselves and have the knowledge needed to make the best choices for themselves that will lead to happiness and good health.

PETITION ON HORMONAL CONTRACEPTIVES

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CONTRACEPTIVE STUDY GROUP

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Preliminary Statement

Hormonal contraceptives have been on the market for over 50 years and, while their formulations have changed, the basic mechanism of action has remained the same. During this time numerous studies have been performed documenting side effects, some of which appear over time, some within weeks or months, but all can have a serious impact on health. An effort was made to perform a series of comprehensive literature surveys to better understand immediate and long-term side effects of these agents. The results of this literature review have led to several recommendations. These recommendations are listed below with the documentation of the research noted on the following pages.

Action Requested

Drugs which should be removed from the market:

- Depot Medroxyprogesterone Acetate (DMPA)
    - Recommendation to remove from the market the injectable contraceptive Depot Medroxyprogesterone Acetate (DMPA; Depo Provera) based on conclusive evidence that it facilitates the transmission of HIV from men to women. Numerous alternatives are available.

Black box warnings that should be added to prescribing information

- Breast Cancer
    - Combined estrogen-progestogen contraceptives (COCs, including oral, intravaginal and transdermal formulations) are acknowledged by IARC as Group I carcinogens. Substantial data supports an increased risk of breast cancer with the use of COCs. A black box warning should be added to the labeling of all COCs that they have been shown to increase the risk of breast cancer. Patient-related materials should also adequately convey this risk.
    - Progestogen-only contraceptives (POCs) have not been extensively studied, but one large registry study did show a significantly increased risk of breast cancer with use of POCs. Unless there is evidence to the contrary, a similar warning should be added to all POCs. Patient-related materials should also adequately convey this risk.
- Cervical Cancer
    - COCs have been linked to a significantly increased risk of cervical cancer. Similar data have been shown for POCs. A black box warning should be added to the labeling of all COCs and POCs that they have been shown to increase the risk of cervical cancer. Patient-related materials should also adequately convey this risk.
- Inflammatory Bowel Disease
    - Significantly higher risk for the development of inflammatory bowel disease, especially Crohn's disease, but also ulcerative colitis, has been shown for COCs. A black box warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk for the development of inflammatory bowel disease. Patient-related materials should also adequately convey this risk.
- Systemic Lupus Erythematosus (SLE)
    - Significantly higher risk for the development of SLE has been shown for COCs in several studies, especially the best-designed, largest cohort studies. A black box warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk of the development of SLE. Patient-related materials should also adequately convey this risk.
- Depression and Suicide
    - Substantive evidence indicates there is a 25% risk of depression for women under 25 years of age especially within 6 months of starting COCs. A black box warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk of the development of depression. Patient-related materials should also adequately convey this risk.
    - The relative risk for suicide attempts ranges from 1.91 for COC's, to 2.29 for oral progestins, 2.58 for vaginal ring and 3.28 for patch among adolescents and young women – mean age 21 years – peaking within two months of onset of medication. A black box warning should be added to the labeling of all COCs that their use is linked to a significantly increased risk of suicide. Patient-related materials should also adequately convey this risk. Close monitoring is essential especially in the first year of use.
- Venous Thrombosis and Cardiovascular Events
    - The current black box warning regarding thrombotic events on some formulations, notes "WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS." This is misleading and has shown to be misinterpreted by many women who infer that the increased risk only occurs with cigarette smoking and/or with being over 35 years of age. The warnings should be amended to state, "WARNING: INCREASED RISK OF SERIOUS CARDIOVASCULAR EVENTS INCLUDING BLOOD CLOTS."

- This warning should be required for hormonal birth control products including oral, intravaginal and transdermal formulations. The patient-related materials should clearly explain the genetic risk factors, other risk factors, and the signs and symptoms. This warning should be included in ALL direct-to-consumer advertising (television, print, radio, etc.).

Additional safety information which should be added

- Multiple Sclerosis (MS)
  - Significantly higher risk for the development of MS has been shown for COCs in several studies, especially the best-designed, largest case-control studies. A warning should be added to the labeling of all COCs that their use appears to be linked to a significantly increased risk of the development of MS. Patient-related materials should also adequately convey this risk.
- Bone Fractures
  - Use of POCs is clearly associated with a higher risk of bone fractures. A warning should be added to the labeling of all POCs that their use is linked to a significantly increased risk of the development of bone fractures. Patient-related materials should also adequately convey this risk.
  - Protracted use of COCs has been associated with an increased risk of bone fractures. A warning should be added to the labeling of all COCs that their prolonged use may be linked to a significantly increased risk of the development of bone fractures. Patient-related materials should also adequately convey this risk.
- Body Mass Effects
  - For ANY progestin-releasing IUD:
    - Add to professional label in side effects/precautions:
      - Progestin-releasing IUDs (IUCs) have demonstrated in clinical trials to significantly increase % fat body mass with a corresponding decrease in % lean body mass over 1 year of use.
    - Add to patient-related materials:
      - Use of (Brand name) may increase the percent of fat in your body while decreasing the percent of lean body mass; this change in body composition is known to increase risk of other serious conditions such as diabetes and cardiovascular problems.
  - This warning should be included in all direct-to-consumer advertising (television, print, radio, etc.) as it demonstrates use of IUCs may contribute to other serious chronic health conditions.
  - Similar labeling should be considered for progestin-only contraceptives. Although the current evidence is less, it tends in the same direction.
- Urogenital Problems
  - Interstitial Cystitis: Significantly higher risk for the development of interstitial cystitis has been shown for COCs in two studies. A warning should be added to the labeling of all COCs that their use appears to be linked to a significantly increased risk of the development of interstitial cystitis. Patient-related materials should also adequately convey this risk.
  - COCs have also been linked to an increased risk of bacteriuria, urinary tract infections, bladder trabeculation, vulvovaginal candidiasis, vaginal dryness, vulvar vestibulitis, and Female Sexual Dysfunction (FSD) caused by OC-induced dyspareunia and reduced sexual desire and libido. These risks should be adequately conveyed in the prescribing information, especially FSD where there is substantial literature evidence.

List of Agents

A list of the agents discussed is shown below. Other than Depot Medroxyprogesterone Acetate (DMPA; Depo Provera) we refer in general to COCs (which refers to all combined estrogen-progestogen contraceptive formulations) and POCs (which refers to all progestin-only contraceptive formulations) regardless of the route of administration (e.g. oral, intravaginal, transdermal, implants, IUS/IUD, etc.).

Combined Estrogen-Progestin (EE-P) Pills

OVCON-35
FEMCON 35
FEMCON FE
BALZIVA 28
BRIELLYN 28
PHILITH
GILDAGIA
VYFEMLA
NEXESTA FE
and generic therapeutic equivalents

BREVICON
MODICON 28
NORMINEST FE
NORTREL 0.5/35-28
WERA
CYCLAFEM
CYONANZ
and generic therapeutic equivalents

GENERESS
KAITLIB FE
and generic therapeutic equivalents

NORINYL 1+35 28-DAY TABLETS
ORTHO-NOVUM 1/35 28 TABLETS
ALYACEN 1/35
ARANELLE
CYCLAFEM 1/35
DASETTA 1/35
NORTREL 1/35-28
NYLIA 1/35
PIRMELLA 1/35
and generic therapeutic equivalents

ORTHO-NOVUM 7/7/7-28
ALYACEN 7/7/7
CYCLAFEM 7/7/7
DASETTA 7/7/7
NORTREL 7/7/7
NYLIA 7/7/7
PIRMELLA 7/7/7
TRI-NORINYL 28-DAY
ARANELLE
NORINYL 1+50 28-DAY
LOESTRIN 21 1/20
LOESTRIN 21 1/20 FE
MINASTRIN 24 FE
TAYTULLA
MIBELAS 24 FE
MICROGESTIN 1/20
MICROGESTIN FE 1/20
JUNEL 1/20
GILDESS 1/20 and GILDESS FE 1/20
LARIN 1/20 and LARIN FE 1/20
BLISOVI 1/20 and BLISOVI FE 1/20
AUROVELA 1/20 and AUROVELA 1/20 FE
HAILEY 1/20 and HAILEY FE 1/20
and generic therapeutic equivalents

LOESTRIN 21 1.5/30
LOESTRIN FE
MICROGESTIN 1.5/30
MICROGESTIN FE
AUROVELA 1.5/30
AUROVELA FE 1.5/30
BLISOVI FE 1.5/30
GILDESS 1.5/30
GILDESS FE 1.5/30
JUNEL 1.5/30
JUNEL FE
LARIN 1.5/30
LARIN FE
ESTROSTEP 21
ESTROSTEP FE
TRI-LEGEST 21
TRI-LEGEST FE
and generic therapeutic equivalents

ZOVIA 1/35E-28
KELNOR
and generic therapeutic equivalents

LOW-OGESTREL-28
CRYSELLE
ELINEST
OGESTREL 0.5/50-28
LoSEASONIQUE
LO SIMPESSE
and generic therapeutic equivalents

ALESSE
LEVLITE
LESSINA-28
AVIANE-28
BALCOLTRA
AFIRMELLE
FALMINA
ORSYTHIA
VIENVA
and generic therapeutic equivalents

QUARTETTE—91-DAY
FAYOSIM
SEASONALE
INTROVALE
ALTAVERA
AYUNA
QUASENSE
SETLAKIN
LEVORA 0.15/30-28
KURVELO
PORTIA-28
MARLISSA
SEASONIQUE
ASHLYNA
DAYSEE
JAIMIESS
SIMPESSE
and generic therapeutic equivalents

TRIVORA-28
ENPRESSE-28
LEVONEST
ELIFEMME
MYZILRA
and generic therapeutic equivalents

DESOGEN
EMOQUETTE
ENSKYCE
ISIBLOOM
KALLIGA
and generic therapeutic equivalents

KARIVA
KIMIDESS
VIORELE
PIMTREA
VOLNEA
BEKYEE
and generic therapeutic equivalents

CYCLESSA
VELIVET
and generic therapeutic equivalents

ORTHO-CYCLEN-28
SPRINTEC
PREVIFEM
MONO-LINYAH
ESTARYLLA
MILI
and generic therapeutic equivalents

ORTHO TRICYCLEN 28
TRI-SPRINTEC
TRIPREVIFEM-28
TRI-LINYAH
TRI-ESTARYLLA
TRI-MILI
and generic therapeutic equivalents

ORTHO TRI-CYCLEN LO
TRI-PREVIFEM
TRI LO SPRINTEC
TRI-LO-ESTARYLLA
TRI-LO-MILI
and generic therapeutic equivalents

YAZ
LORYNA
NIKKI
MELAMISA
LO-ZUMANDIMINE
and generic therapeutic equivalents

BEYAZ
and generic therapeutic equivalents

YASMIN 28
SYEDA
YAELA
ZUMANDIMINE
and generic therapeutic equivalents

SAFYRAL
NATAZIA

Combined EE-P Contraceptive Patch

ORTHO EVRA
XULANE

Combined EE-P Contraceptive Ring

NUVARING

Progestin-Only Pills

MICRONOR TABLETS
NOR-QD TABLETS
CAMILA
ERRIN
HEATHER
JENCYCLA
INCASSIA
and generic therapeutic equivalents

Progestin-Only Injectable

DEPO PROVERA

Progestin-Only Implants

JADELLE
NEXPLANON

Progestin-Only IUS/IUD

MIRENA IUS
LILETTA IUD
SKYLA IUD
KYLEENA IUD

Statement of Grounds

Risk of HIV Transmission

One of the most common forms of steroidal contraception is the injectable contraceptive: Depot medroxyprogesterone acetate (DMPA). DMPA is highly effective and requires only quarterly injections, as opposed to daily oral ingestion. As a long-acting type of effective contraceptive, it is not unique, as there are other injectable or implantable contraceptives in wide use, e.g., norethisterone enanthate (NET), as well as other delivery systems such as vaginal rings and patches.

However, evidence began emerging in the 1990s, which has become compelling in recent years, that DMPA is unique among contraceptives in its property of facilitating the transmission of HIV. This dangerous characteristic has been abundantly and unequivocally documented through several lines of evidence which are summarized below:

Epidemiological Evidence

A. Four meta-analyses (3 reports) were published in 2015. Each used different inclusion criteria and compiled the data on different numbers of studies, yet all 4 came up with essentially the same result of significantly increased risk of male-to-female HIV transmission in women using DMPA (Table 1).

Table 1 – Meta-Analyses Evaluating Risk of HIV Transmission with Depot medroxyprogesterone acetate (DMPA)

Meta-analysis	# Included studies	Pooled Adj. OR or HR (95% CI)
Ralph et al. 2015	10 (longitudinal)	HR 1.40 (1.16–1.69)
Morrison et al. 2015	18 (longitudinal)	HR 1.50 (1.24–1.83)
Brind et al. 2015	8 (cross-sectional)	OR 1.41 (1.15–1.73)
Brind et al. 2015	16 (longitudinal)	HR 1.49 (1.28–1.73)

B. Ten primary studies (all longitudinal, published between 2003 and 2014, listed in
C. Table 2 below) were methodologically robust enough to meet the inclusion criteria of all 3 published reviews.

Table 2 – Individual Studies of the Effects of DMPA HIV Transmission

Study	Yr.(s) of study	Pop. size	Nation and locale	Subject source	Months of follow-up	Follow-up interval (months)	Type of data shown	HR or IRR (95% CI)	Weight (%)
Crook 2014	2005–2009	8,663	S Africa, Uganda, Tanzania, Zambia	Microbicide trial sero-disc. couples	12	1	Inv. Prob. W'ted HR	1.45 (1.09–1.93)	16.39
McCoy 2013	2003–2007	4,913	South Africa, Zimbabwe	Diaphragm/gel HIV prev. trial	24	3	MV HR	1.22 (0.85–1.76)	13.20
Morrison 2012	2004–2007	5,567	South Africa	General population	9–24	3	MSM HR	1.27 (0.93–1.73)	15.32
Wand 2012	Not reported	2,236	Durban, S. Africa	>90% from microbicide trial	Not reported	3	MV HR	2.02 (1.37–2.99)	12.22
Heffron 2012	2004–2010	3,790	7 African nations	Sero-discordant couples	12–24	3	MSM HR	3.93 (1.38–11.21)	2.81
Morrison 2007	1999–2004	6,109	Uganda, Zimbabwe, Thailand	Family planning clinics	21.5	3	MSM HR	1.25 (0.88–1.77)	13.86
Myer 2007	2000–2004	4,073	Cape Town, So. Africa	General population	24	6,6, & 12	MV IRR	0.75 (0.33–1.69)	4.36
Kleinschmidt 2007	1999–2001	551	Orange Farm, So. Africa	Family planning clinic	12	3	MV HR	0.46 (0.06–3.66)	0.78
Baeten 2007	1993–1997	779	Mombasa, Kenya	CSW	120	1	MV HR	1.73 (1.28–2.34)	15.69
Kiddugavu 2003	1994–1999	5,117	Rakai, Uganda	General population	31	10	IRR, MLR	0.84 (0.41–1.72)	5.37

Importantly, no consistent association has emerged with regard to oral contraceptives or other injectable or implantable contraceptives and the facilitation of HIV transmission.

Mechanistic Evidence

A. *In vivo* evidence of increased HIV transmission: Heffron et al. (2012) reported the increased presence of HIV-1 RNA in genital fluids of women using DMPA.
B. *In vitro* evidence of increased HIV replication at the cellular level: Maritz et al. (2018) reported experimental evidence of increased replication of HIV in human blood monocytes with medroxyprogesterone acetate (MPA).

C. Experimental evidence of agonistic binding to the glucocorticoid receptor (GR) as the mechanism for DMPA's immunosuppression: over the last 15 years, abundant experimental evidence of cytotoxic and immunosuppressive action of DMPA via its agonistic binding to the GR of human leukocytes has been reported (Schindler 2003; Hapgood and Tomasicchio 2010, Hapgood 2014.) Thus, Huijbregts et al. (2014) reported experimental evidence of immunosuppression of human T cells in vitro by MPA. Tomasicchio et al. (2013) reported experimental evidence of increased human T-cell destruction in vitro via the glucocorticoid receptor (GR) with MPA. Hapgood et al. (2014) reported:

> *"that MPA, unlike NET and progesterone, represses inflammatory genes in human PBMCs (peripheral blood mononuclear cells) in a dose-dependent manner, via the glucocorticoid receptor (GR), at concentrations within the physiologically relevant range. These and published results collectively suggest that the differential GR activity of MPA versus NET may be a mechanism whereby MPA, unlike NET or progesterone, differentially modulates HIV-1 acquisition and pathogenesis in target cells where the GR is the predominant steroid receptor expressed."*

D. Evidence of mechanism of MPA action at the gene expression level: experimental evidence of MPA-mediated suppression of inflammatory genes via GR in cultured human cells (Govender 2014) demonstrated the suppression of inflammatory genes in cultured human endocervical cells.

Summary and Conclusions:

DMPA, in contrast to all other steroidal contraceptives, has now conclusively been demonstrated to significantly increase the risk of HIV transmission from infected men to women. The robust epidemiological association has been supported by *in vivo* evidence of increased HIV RNA in the female genital tracts of women using DMPA. Moreover, abundant experimental evidence has shown that MPA, due to its agonistic binding of the GR, specifically represses the innate immune responses of both circulating human leukocytes and endocervical cells and allows for increasing HIV replication. The demonstration in the literature of the chain of causation is therefore compelling.

In the United States, where the availability of a wide range of contraceptive drugs and devices is virtually universal, and where, among these contraceptive choices, one and only one particular method—DMPA—is now known to increase the transmission of an often-fatal viral infection (HIV/AIDS), there can be no justification for such a drug's continued availability in the marketplace. It should be removed from the marketplace by the FDA without further delay.

Postscript Re: Petition for removal of DMPA from US market due to increased risk of HIV transmission:

New ECHO Trial study presents confirmation disguised as refutation

Three systematic reviews and meta-analyses (SRMAs) of studies on the risk of HIV acquisition of HIV infection by women using DMPA were published in 2015. One of them (Morrison 2015) concluded that their analysis "adds to the evidence that DMPA may increase HIV risk." They further suggested that "A randomized control trial would provide more definitive evidence about the effects of hormonal contraception, particularly DMPA, on HIV risk."

On June 13 of this year, the results of precisely such a randomized control trial were published in the Lancet by the ECHO Trial Consortium, the trial having been designed by a group of ten that includes 3 of the authors of the 2015 Morrison SRMA (Morrison, Baeten and Rees). However, in stark contrast to their 2015 conclusion, the ECHO group, which studied DMPA in comparison to the copper IUD and the levonorgestrel (LNG) implant, concluded: "We did not find a substantial difference in HIV risk among the methods evaluated, and all methods were safe and highly effective."

However, a careful analysis of the design and results of the ECHO Trial reveals that in fact, the ECHO Trial results of 2019 provide a near perfect confirmation of the results of the 2015 Morrison SRMA, and that the authors misrepresent them as the opposite; as the exculpation of DMPA as "safe".

The performance of an appropriate randomized control trial presented the ECHO Trial Consortium with serious ethical and scientific challenges. First, the very idea of the need to conduct such a trial of a medical drug or device for an elective condition (contraception) which had already been shown to present significant risk elevation for the contraction of a potentially life-threatening infection (HIV) by three independent SRMAs, reviewing data that had been accumulated in dozens of studies dating back over a quarter century, is ethically problematic, to say the least. This is especially true in the case of DMPA, a contraceptive progestin that stands alone among many such available, in its property of being a glucocorticoid agonist, the likely mechanism by which it increases HIV risk. Indeed, the Morrison SRMA was the most mildly worded of the three 2015 SRMAs, with that of Ralph et al. suggesting that the risk might "merit complete withdrawal of depot medroxyprogesterone acetate" from the market, and that of Brind (2015), concluding that the evidence that DMPA increases the risk of HIV transmission was now "compelling".

Secondly, assuming that conducting such a study at all would be ethically valid, the WHO (2017) changed the guidance for use of DMPA from category 1 ("no restriction") to category 2 ("a condition where the advantages of using the method generally outweigh the proven or theoretical risks"), relating to the use of DMPA as a contraceptive in women at high risk of HIV acquisition. This guidance was based on the three 2015 SRMAs. At the very least, this new WHO guidance would need to be disclosed to all the ECHO

study subjects, and the ECHO study notes that all participants in the study "were provided with this updated information". But the providing of such information presents a clear ethical challenge itself, in the context of a trial wherein subjects are randomly assigned to one of three groups, only one of which was clearly already known to facilitate HIV transmission. What of women who were assigned to the DMPA group? On the one hand, advising them that they were now in the highest risk group regarding HIV infection would unblind them and likely encourage them to opt out of the study, thus rendering the study scientifically invalid. On the other hand, not so advising these women would constitute withholding information on the risks of the proposed medication, a clear violation of the need to obtain informed consent. Determined to conduct a scientifically valid study, it would seem, the ECHO Consortium opted to make "concerted efforts to not provide additional or differential information or counseling to women in the DMPA-IM group."

Thirdly, assuming (*arguendo*) that the ethical challenges have been adequately met by the study design, there is the challenge of scientific validity. In such a trial a critical aspect of study design is the statistical power of the study; to ensure that the statistical power is adequate to either confirm or reject the earlier findings. As noted in our petition, the three 2015 SRMAs arrived at virtually the same results, in the comparison of women using DMPA to those using no form of hormonal contraception. The results obtained by Morrison et al. included an overall HR = 1.50 (95% CI 1.24-1.83). But Morrison et al. also compared DMPA use to combined oral contraceptive (COC) use: HR = 1.43 (95% CI 1.23-1.67) and to use of the injectable progestin norethisterone enanthate (NET-EN). In contrast, there was no significant increase in HIV infection risk with either NET-EN (HR = 1.24; 95% CI 0.84-1.82) or COC use (HR = 1.03; 95% CI 0.88-1.20). Importantly, they also compared the use of each of the three methods to each other, and they reported that, compared to NET-EN, DMPA use was still associated with significantly elevated HIV infection risk: HR = 1.32 (95% CI 1.08-1.61). In the new ECHO study, three contraceptive methods (DMPA, copper IUD and LNG implants) were compared only to each other. Therefore, the key comparison (in regard to DMPA) was clearly between the effects of DMPA v. the effects of LNG, another long-acting, progestin only contraceptive steroid, and one which, like NET-EN and unlike DMPA, has neither been found to significantly elevate HIV infection risk, nor to interact with the glucocorticoid receptor. Since the appropriate comparison in the 2015 Morrison SRMA was between DMPA and NET-EN use, a perfect replication of the result they obtained thereby would be a statistically significant elevation in the neighborhood of HR = 1.3. Hence it is puzzling that the ECHO study was statistically designed thus:

"The trial was designed with 80% power to detect a 50% increase in the hazard of HIV for each contraceptive method compared with each of the others (ie, DMPA-IM *vs* copper IUD, DMPA-IM *vs* LNG implant, and copper IUD *vs* LNG implant). We chose a 50% increase in HIV risk on the basis of formative work with stakeholders to determine a meaningful difference that would inform policy change."

In other words, the ECHO consortium was not concerned with the scientific imperative of repeating or refuting their earlier results. Rather, they had made the decision that anything less than a 50% increase in HIV infection risk was not "a meaningful difference", thus to be ignored. Not surprisingly then, the result obtained in the ECHO study, comparing DMPA use to LNG use, was (in their "continuous use" dataset, Table 2 in ECHO 2019), HR = 1.29 (95% 0.98-1.71). Therefore, although this result is virtually identical to the result Morrison et al obtained in their 2015 SRMA, it just failed to achieve statistical significance at the 0.05 level (p=0.06), due to the study's having been underpowered to detect this difference.

Yet the ECHO Consortium seized upon this result to call DMPA "safe and effective" (along with the other two methods tested), and their literal bottom line conclusion was: "These results support continued and increased access to these three contraceptive methods."

From both a scientific and an ethical point of view, this conclusion is clearly erroneous. Six women died in the DMPA group out of the 2609 enrolled, compared to only one death in the LNG group (There were 143 v 116 cases of HIV infection in the DMPA v. LNG, respectively.) Thus DMPA appeared responsible for 5 excess deaths (and 27 excess cases of HIV infection); about 0.19% of its users, in a maximum follow-up period of only 12-18 months (average 1.33 years follow-up for the 7829 women participating with a total of 10,409 woman-years of follow-up time). If a woman's reproductive life is estimated to be about 25 times the follow-up period, from age 13 until about age 45, that would come out to a death rate of about 5% of women using DMPA compared to other injectable or implantable progestins over the course of their fertile years. The excess rate of HIV acquisition would likely cause far more excess deaths. This increased risk of death is clearly not acceptable.

We can see no justification whatsoever for the continued availability of DMPA in the US market. This detailed analysis of the ECHO Consortium study only underscores our earlier conclusion.

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Cancer

Papers were accessed from a PubMed literature review as noted (Williams 2018). Each paper was rated based on the parameters noted in the STROBE statement (von Elm et al. 2007).

Breast Cancer

Breast cancer is the most commonly diagnosed cancer (excluding non-melanoma skin cancers) in women in developed nations, including the U.S., with 1.7 million cases diagnosed worldwide annually. It accounts for 20% of all cancers in women.[1] According to the Surveillance, Epidemiology and End Results (SEER) statistics[2], it is estimated that there are about 3,418,000 women with invasive breast cancer in the USA as well as over 60,000 cases of in situ cancers. There will be about 266,000 new cases of breast cancer in 2018, accounting for 15.3% of all new cancer cases, with about 41,000 deaths, accounting for 6.7% of all cancer deaths. Nulliparity or late childbearing and high body mass index are risk factors for breast cancer as is exposure to COCs and HRT. Any risk factors that are controllable should be minimized. The data for breast cancer is shown split into cohort studies (Table 3), case control studies (Table 4) and meta-analyses (Table 5).

The carcinogenicity of combined estrogen-progestogen contraceptives was evaluated by IARC working groups initially in 1998 (monograph published in 1999) and again in 2005 (monograph published in 2007). This was most recently updated with studies published through May 2008 (IARC 2012). Since that time, several important studies have been published, most of which are supportive of the IARC classification of COCs as Group I carcinogens and in agreement with the IARC evaluation of specific cancer types. In addition, several important studies have been published evaluating COCs and their cancer risk. In 2002 the National Toxicology Program added steroidal estrogen as a known human carcinogen (Report on Carcinogens, Fourteenth Edition available at https://ntp.niehs.nih.gov/pubhealth/roc/index-1.html).

In agreement with IARC the recent data confirms an increased risk of breast cancer with use of COCs (Table 2). After 2005, there continue to be studies demonstrating the significant risk of breast cancer with hormonal contraception. In January 2006, the *New England Journal of Medicine* published a review article which found estrogen-progestin drugs increased breast cancer risk (Yager 2006). In October 2006 the *Mayo Clinic Proceedings* published a meta-analysis confirming estrogen-progestin drugs increase premenopausal breast cancer (Kahlenborn 2006).

The studies that looked at recent use (within 1–5 years) or current use of COCs in premenopausal women showed the most dramatic increased risk for breast cancer. In a case control study, women ages 20-49 years with use of COCs within a year had an increased risk of breast cancer (OR, 1.5; 95% CI, 1.3–1.9) (Beaber 2014). The same study showed an increase in risk depending on the formulation with triphasic COCs carrying a markedly increased risk (OR, 3.1; 95% CI, 1.4–4.7). In another large case control study of women ages 20-45 years, use of COCs for a year or more resulted in a 2.5-fold increased risk of triple-negative breast cancer (95% CI 1.4–4.3) but not for the receptor-positive breast cancers. In the same study, women 40 years or younger with a year or more use of COCs had a higher relative risk of triple-negative breast cancer (RR, 4.2; 95% CI, 1.9–9.3) (Dolle 2009). A cohort study of over 35,000 postmenopausal women found a significantly increased risk of breast cancer in women on hormone replacement therapy (HRT) if they had used COCs in the past (RR, 2.45; 95% CI, 1.92–3.12) as compared with never users (RR, 1.67; 95% CI, 1.32–2.12) (Lund 2007). There also appears to be an increased risk for African American women on COCs within the past five years for ER+ cancers (OR, 1.46, 95% CI, 1.18–1.81), for ER- cancers (OR, 1.57; 95% CI, 1.22–1.43) and for triple-negative cancers (OR, 1.78; 95% CI, 1.25–2.53) with the risk of ER+ cancers continuing for 15–19 years after stopping the COCs (Bethea 2015).

In a French study (DeLort 2007) of 934 women who developed breast cancer, the use of COCs increased the risk of early development of breast cancer (OR, 1.84; 95% CI, 1.38–2.44). However, initiating COCs after age 23 reduced the risk (OR, 0.52; 95% CI, 0.34–0.79). Use of the levonorgestrel-releasing IUD, commonly used to treat abnormal bleeding in the perimenopause, increased the risk of developing breast cancer in postmenopausal women (OR, 1.48, 95% CI, 1.10–1.99) (Heikkinen 2016). The risk varies with the formulation as current use of a triphasic pill containing levonorgestrel carries an excess risk of causing breast cancer (RR, 3.05; 95% CI, 2.00–4.66) (Hunter 2010). In a large prospective cohort study of 1.8 million Danish women ages 15 to 49, enrolled and followed from 1995 to 2012 through various national registries, the risk of breast cancer among current or recent users increased depending on length of use from RR, 1.09 with less than one year of use (95% CI, 0.96–1.23) to an RR, 1.38 (95% CI, 1.26–1.51) for more than 10 years of use (Mørch 2017). They found the increased risk persisted after discontinuing use if COCs were used for 5 years or more. These investigators also found an increased risk in current or recent use of the progestogen-only intrauterine device (RR, 1.21; 95% CI, 1.11–1.33).

In most Western countries, 5% to 10% of all breast cancer cases are due to a main genetic cause: mutations of the BRCA1 and BRCA2 genes constitute 90% of hereditary breast cancer cases (Mehrgou 2016). These women are often begun on COCs at an early age to reduce their risk of ovarian cancer. However, in a case control study of 2,492 matched pairs of women with the *BRCA1* gene, COC use was associated with an increased risk of early onset breast cancer if begun under the age of 20 (OR, 1.45; 95% CI, 1.20–1.75) (Kotsopoulos 2014) and the risk increased by 11% for each additional year of use.

More recent publications include data from some very recent, large cohort studies (Mørch 2017, Heikkinen 2016, Poosari 2014) with RRs ranging from 1.2 to 1.37. Since breast cancer is by far the most common cancer in women, affecting 1 in 8 women at some time

[1] https://www.wcrf.org/int/cancer-facts-figures/data...cancers/breast-cancer-statistics.
[2] https://seer.cancer.gov/statfacts/html/breast.html.

during their lives, this translates into a substantial number of additional cancer cases. In addition, a large registry study of POCs (Soini 2014) also showed an increased RR for breast cancer of 1.19. Increased duration of use also increases the risk of breast cancer for COCs as does use early in life (Mørch 2017).

Table 3 – Breast Cancer (Cohort Studies)

Study	Study Design	OR[3] Ever Use	RR[4] Ever Use	OR Current Use	RR Current Use	Cases	Controls	Quality Score
Mørch et al. 2017	Cohort		1.2[5] (1.14–1.26)			1,797,932	*[6]	100%
Heikkinen et al. 2016	Cohort		1.37 (1.12–1.68)			7,000	20,000	100%
Lund et al. 2007	Cohort		1.33 (1.11–1.59)			11,777	23,676	96%
Poosari et al. 2014	Cohort		1.31 (0.65–2.65)			70	11,344	92%
Phipps et al. 2011	*[7]		0.80[8] (0.68–0.94)			5,194		92%
Brohet et al. 2007[9]	Cohort		1.47 (1.16–1.87)			846	747	88%
Thorbjarnardottir et al. 2014	Cohort		1.32 (1.02–1.70)			654	16,928	84%
Samson et al. 2017	Cohort		1.80[10] (1.29-2.55)			4816		83%
Rosenberg et al. 2010	Cohort		1.65 (1.19–2.30)			789	53,848	83%
Silvera et al. 2005	Cohort		0.88[11] (0.73–1.07)			1,707	25,611	78%
Hunter et al. 2010	Cohort		1.12 (0.95–1.33)		1.33 (1.03–1.73)	1,344	115,264	73%
			1.42[12] (1.05–1.94)					
			3.05[13] (2.00–4.66)					
Trivers et al. 2007[14]	Cohort			1.57 (0.95–2.61)		292[15]	1,264[16]	67%

[3] OR = odds ratio (95 % confidence interval).
[4] RR = relative risk (95 % confidence interval).
[5] Initiation before age 20, greater than 10 years of use and evaluation within 5 yrs. of stopping further increased the risk.
[6] Entire population of Denmark was the cohort.
[7] Concurrent randomized clinical trials and an observational study.
[8] Hazard ratio shown. Note that women started COCs after age 25, had been off COCs for many years.
[9] Evaluation in patients carrying BRCA mutations. Hazard ratios shown.
[10] Hazard ratio shown.
[11] Hazard ratio shown.
[12] Eight or more years of use.
[13] Levonorgestrel containing combined oral contraceptives.
[14] Looked at mortality in patients with breast cancer over 8-10 years depending on whether they were on COCs at the time of diagnosis or within one year.
[15] Deaths.
[16] Total cohort.

Table 4 – Breast Cancer (Case Control Studies)

Study	Study Design	OR[17] Ever Use	RR[18] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Dolle et al. 2009	Case control	2.5 (0.9-5.24)		4.2 (1.9-9.3)				898	961	100%
Lee et al. 2008	Case Case[19]	0.68 (0.33-1.38)						94	444	100%
Sweeney et al. 2007	Case control	1.27 (0.99-1.63)						2,318	2,515	100%
Beaber et al. 2014b	Case control	1.5 (1.1-2.2)						985	882	100%
Li et al. 2012[20]	Case control	2.2 (1.2-4.2)						1,028	919	96%
Beaber et al. 2014a	Case control			1.5[21] (1.3-1.9)				1,102	21,952	96%
Ichida et al. 2015	Case control			0.45 (0.22-0.90)				155	12,333	96%
Ma et al. 2010	Case control	2.87[22] (1.44-5.74)						1,197	2,015	95%
Folger et al. 2007	Case control	1.0[23] (0.8-1.1)						4575	4682	92%
Jernstrom et al. 2005	Case control					2.10 (1.32-3.33)		245	745	92%
Kotsopoulos et al. 2014[24]	Case control	1.45[25] (1.20-1.75)						2,492	2,492	88%
		1.19[26] (0.99-1.42)								
Figueiredo et al. 2010[27]	Case control					2.38 (0.72-7.83)		705	1,398	86%
Veneroso et al. 2008	Case Case[28]	1.12 (1.03-1.23)						116	99	86%
Ma et al. 2006	Case control	1.27[29] (0.75-2.14)				0.76 (0.49-1.18)		1,366	440	84%
		0.76[30] (0.49-1.18)								
Rosenberg et al. 2008	Case control	1.5[31] (1.2-1.8)						907	1,711	83%
Haile et al. 2006	Case control	0.77[32] (0.53-1.12)						195	497	83%
		1.62[33] (0.90-2.92)						128	307	

[17] OR = odds ratio (95 % confidence interval).
[18] RR = relative risk (95 % confidence interval).
[19] BRCA1 and BRCA2 carriers with breast cancer.
[20] Population-based case-control of women 20-44 yo with recent DMPA use for at least 12 months.
[21] Use within the past year of COCs increases risk of breast cancer.
[22] Triple negative breast cancer if less than 18 yo on COCs.
[23] Evaluated short-term use only.
[24] Study of BRCA+ patients.
[25] <20 years old.
[26] 20-25 years old.
[27] Evaluation of BRCA1 and BRCA2 carriers; controls with unilateral breast cancer compared with contralateral cases.
[28] Comparison of more aggressive with less aggressive cases.
[29] ER-/PR-
[30] ER+/PR+
[31] OR for 5+ years of use.
[32] BRCA1+ patients.
[33] BRCA2+ patients.

Study	Study Design	OR[17] Ever Use	RR[18] Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Milne et al. 2005	Case control	1.52 (1.22-1.91)						1156	815	83%
Amadou et al. 2013	Case control	1.68 (0 .67-4.21)						1,000	1,074	75%
Ozmen et al. 2009	Case control	0.60 (0.48-0.74)						1,492	2,167	74%
Delort et al. 2007	Population based[34]	1.84[35] (1.38-2.44)						934		71%
Beji et al. 2006	Case control	1.98 (1.38-2.85)						405	1,050	63%
Veisy et al. 2015	Case control	2.11 (1.44-3.08)						235	235	63%
Tehranian et al. 2010	Case control	2.83 (1.87-4.24)						321	321	58%
Lumachi et al. 2010	Retrospective Review	2.06 (1.14-3.70)						404	408	33%

Table 5 – Breast Cancer (Meta-Analyses)

Study	Study Design	OR[36] Ever Use	Cases	Controls	Quality Score
Kahlenborn et al. 2006[37]	Meta-analysis	1.19 (1.09-1.29)	18,406	27,677	91%
		1.29[38] (1.20-1.40)			
		1.24[39] (0.92-1.67)			
		1.44[40] (1.28-1.62)			
Bethea et al. 2015	Meta-analysis	1.46[41] (1.18-1.81)	1,848	10,044	85%
		1.57[42] (1.22-1.43)	1,043	10,044	
		1.78[43] (1.25-2.53)	494	10,044	
Zhu et al. 2012	Meta-analysis	1.08[44] (0.99-1.17)			54%
Friebel et al. 2014[45]	Meta-analysis	1.36[46] (0.99-1.88)			27%
		1.51[47] (1.10-2.08)			
Moorman et al. 2013	Meta-analysis	1.21[48] (0.93-1.58)			

[34] Population-based study of early onset breast cancer.
[35] OR for developing breast cancer 2 years earlier than non-users.
[36] OR = odds ratio (95 % confidence interval).
[37] Limited to case-control studies from 1980-2004.
[38] Parous women.
[39] Nulliparous women.
[40] Use before first full term pregnancy among parous women.
[41] ER+
[42] ER-
[43] Triple negative.
[44] For each 5 years on COCs the risk increased by 7%, but statistical significance not achieved.
[45] Study limited to BRCA1 and BRCA2 mutation carriers.
[46] 1-3 years of use.
[47] >3 years of use.
[48] 8 studies on BRCA1+ or BRCA2+ patients and breast cancer risk with CSC use.

Breast Cancer References

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Cervical Cancer

According to the SEER statistics[49], it is estimated that there are 257,524 women in the US with cervical cancer. There will be about 13,000 new cases of cervical cancer in 2018, with about 4,000 deaths. The five-year survival for cervical cancer is 66%. The IARC evaluation of an increased risk of cervical cancer with COCs is also supported especially by a large, high-quality cohort study (Roura 2016, Table 6). The data for cervical cancer presented in Table 4 shows in particular a higher risk for invasive cervical cancer, and a higher risk with current use. All studies appear to agree that there is an increased risk of cervical cancer in users of COCs (OR apparently about 1.05 per year of use), and this risk increases with duration of use. Current use appears to confer a higher risk than past use, and the risk for invasive cancer shows the highest increase in risk (Roura 2016). A meta-analysis of case-control studies that focused on patients positive for human papilloma virus DNA (Moreno 2002) also showed an increased risk, especially with protracted (5+ years) of use of COCs. One case-control study (McFarlane-Anderson 2008) and one meta-analysis (International Collaboration 2007) also showed an increased risk with progestogen-only contraceptives. Thus, there does appear to be an increased risk of cervical cancer in users of COCs or POCs, and the risk appears to increase with duration of use.

Table 6 – Cervical Cancer

Study	Study Design	OR Ever Use	RR Ever Use	RR Current Use	RR Past Use	Cases	Controls	Quality Score
Roura et al. 2016	Cohort Study		1.1[50] (0.9–1.3)	1.8[10] (1.4–2.4)	1[10] (0.9–1.3)	1,065	306,971	94%
			1.6[51] (1.1–2.3)	2.2[8] (1.3–4.0)	1.6[8] (1.1–2.2)	261	306,971	
Leslie et al. 2014	Case Control Study	1.35[52] (0.99-1.85)				219	2,300	87%
McFarlane-Anderson et al. 2008	Case Control Study	1.59[53] (0.87-2.82)				240	102	83%
		2.48[54] (1.30-4.74)						
Vanakankovit et al. 2008	Case Control Study	1.49 (0.79-2.64)				60	180	76%
Wilson et al. 2013	Case Control Study	1.22 (0.96–1.56)				724	3,479	76%
Matos et al. 2005	Case Control Study	1.3 (0.8–3.1)				140	157	47%

[49] https://seer.cancer.gov/statfacts/html/corp.html
[50] Includes Cervical Intraepithelial Neoplasia Grade 3, carcinoma in situ and invasive cervical cancer.
[51] Analysis limited to invasive cervical cancer.
[52] Study limited to HIV+ women.
[53] Combined hormonal contraceptives.
[54] Progesterone only contraceptives.

Study	Study Design	OR Ever Use	RR Ever Use	RR Current Use	RR Past Use	Cases	Controls	Quality Score
International Collaboration 2007[55]	Meta-analysis	1.0556 (1.04–1.07)				16,573	35,509	97%
	<5 years of use	0.96 (0.04)57						
	5-9 years of use	1.2 (0.05)5						
	10+ years of use	1.56 (0.08)5						
	<5 years of use	1.07 (0.08)58				7,227	19,335	
	5+ years of use	1.22 (0.11)6						
Moreno 2002[59]	Meta-analysis					1676	255	95%
	Invasive cervical cancer (ICC)	1.29 (0.88-1.91)						
	ICC 5+ years of use	4.01 (2.01-8.02)						
	In situ carcinoma (ISC)	1.42 (0.99-2.04)						
	ISC 5+ years of use	3.42 (2.13-5.48)						

Cervical Cancer References

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[55] Meta-analysis of 24 studies (15 cohort and 9 case-control studies).
[56] Relative risk per year of use for current users of combined hormonal contraceptives.
[57] Floating standard error shown for users of combined hormonal contraceptives.
[58] Progestin only contraceptives. Floating standard error shown. The 95% CI for 5+ years of use is 1.01-1.46.
[59] Pooled data from 8 case-control studies of invasive cervical cancer and 2 of carcinoma in situ, analyzing only the subset positive for Human Papilloma Virus DNA in cervical cells.

Crohn's Disease

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

Overall, 17 primary studies and two meta-analyses were identified which evaluated the effect of COCs on the later development of Crohn's disease (Table 7). Of the 17 primary studies, 4 showed a significantly increased risk for either ever use (Ng 2012, Sicilia 2001, Katschinski 1993) or current use (Katschinski 1993, Khalili 2013) or past use (Khalili 2013). None of the primary studies showed a significantly decreased risk. One meta-analysis (Godet 1995) gave a significantly increased RR of 1.44 (95% CI 1.12–1.86) for ever use of COCs. A meta-analysis published in 2008 showed a significantly increased risk for current use (RR of 1.46 [1.26–1.70]) compared with 1.04 (0.816–1.340) for past use. Recent studies have produced similar findings as older studies, with the highest OR published in 2012 (9.04 [1.11–73.6]). Overall these studies indicate that use of COCs conveys an increased risk of Crohn's disease, especially current use.

Table 7 – Individual Studies of the Effects of COCs on the Development of Crohn's Disease

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Khalili et al. 2013[60]	Cohort		1.43		2.82 (1.65–4.82)		1.39 (1.05–1.85)	315	117,060	93%
García Rodríguez et al. 2005[61]	Cohort				1.94 (0.85–4.45)		1.04 (0.50–2.17)	171	10,000	88%
Logan and Kay 1989	Cohort		1.7 (0.88–3.2)					42	45,958	54%
Vessey et al. 1986[62]	Cohort				1.33			18	17,014	46%
Boyko et al. 1994	Case-control		2 (1.0–3.7)					91	169	94%
Katschinski 1993[63]	Case-control				2.5 (0.75–4.6)					93%
Katschinski 1993[64]	Case-control				3.1 (1.1-6.7)					93%
Lashner et al. 1989	Case-control	1 (0.46–2.16)		0.73 (0.34–1.59)		1.8 (0.61–5.29)		51	51	88%
Lesko et al. 1985[65]	Case-control		1.7 (1.0–3.2)					57	2189	83%
Sandler et al. 1992	Case-control		1.49 (0.99–2.26)					184	217	81%
Persson et al. 1993	Case-control		1.7 (0.9–3.2)					152	305	81%
Halfvarson et al. 2006[66]	Case-control				1.5 (0.4–5.3)			102	102	75%
Lowe et al. 2009[67]	Case-control		1.05					21,172	754,6131	74%
Ng et al. 2012[68]	Case-control	4 (1.1–14.2)						125	125	74%
Ng et al. 2012[69]	Case-control	9.04 (1.11–73.6)								74%

[60] Hazard ratios (RR adjusted for time).
[61] OR increased with duration of use.
[62] Authors' calculation adjusted for smoking.
[63] Adjusted RR for 1-3 years prior to disease onset.
[64] Adjusted RR for >3 years prior to disease onset.
[65] RR is from multiple logistic regression analysis.
[66] Monozygotic and dizygotic twins.
[67] Adjusted incidence rate ratio.
[68] Twins study.
[69] Multivariate analysis.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Sicilia et al. 2001	Case-control	2.8 (1.01–7.77)						103	103	71%
Corrao et al. 1998	Case-control ever use			3.4 (1.0–11.9)		1.8 (0.4–7.3)		225	225	67%
Katschinski 1993[70]	Case-control		4.3 (1.3-14.4)					83	83	57%
Han et al. 2010	Case-control		0.66 (0.38–1.15)					315	536	52%
Calkins et al. 1986[71]	Case-control	1.14 (0.44–2.96)						66	67	42%
Calkins et al. 1986[72]	Case-control	1.6 (0.59–4.37)						66	71	42%
Vcev et al. 2015	Case-control	0.28 (0.03–2.46)						11	42	31%
Cornish et al. 2008	Meta-analysis				1.46 (1.26–1.70)		1.04 (0.816–.340)	1251	74,564	91%
Cornish et al. 2008[73]	Meta-analysis				1.58 (1.07–2.40)					91%
Godet et al. 1995[74]	Meta-analysis		1.44 (1.12–1.86)					531	49,156	82%

Crohn's Disease References

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[70] RR for use >3 years.
[71] Hospital controls.
[72] Neighborhood controls.
[73] High quality studies.
[74] Adjusted for smoking.

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Ulcerative Colitis

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

Overall 14 primary studies and one meta-analysis were identified which evaluated the effect of COCs on the later development of ulcerative colitis (Table 8). None of the primary studies has shown a statistically significant decrease in risk, while two showed a significant increase in risk for the development of ulcerative colitis with ever use of COCs (Boyko 1994, Parrello 1997). One meta-analysis examined ever use and failed to show a significant difference (Godet et al. 1995), while another meta-analysis examined current use and found a significantly increased relative risk of 1.28 (1.06–1.54). Overall these studies suggest that use of COCs conveys an increased risk of ulcerative colitis, especially current use.

Table 8 – Individual Studies of the Effects of COCs on the Development of Ulcerative Colitis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Khalili et al. 2013[75]	Cohort		1.18 (0.92–1.52)		1.22 (0.74–2.07)		1.18 (0.91–1.52)	392	116,983	93%
García Rodríguez et al. 2005	Cohort				1.58 (0.71–3.52)		0.67 (0.32–1.39)	222	10,000	88%
Logan and Kay 1989	Cohort		1.3 (0.82–2.0)					78	45,922	54%
Vessey et al. 1986[76]	Cohort				2.1			31	17,001	46%
Boyko et al 1994	Case-control		1.7 (1.1–2.7)					211	341	94%
Lashner et al. 1990	Case-control	0.86 (0.40–1.85)		0.7 (0.27–1.83)		1.14 (0.41–.15)		46	46	81%

[75] Hazard ratios (RR adjusted for time).
[76] Authors' calculation, adjusted for smoking.

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Sandler et al. 1992[77]	Case-control		1.1 (0.65–1.85)					89	217	81%
Persson et al. 1993	Case-control		1.7 (0.8–3.3)					145	305	81%
Halfvarson et al. 2006[78]	Case-control				0.6 (0.1–2.5)			125	125	75%
Ng et al. 2012[79]	Case-control	0.43 (0.11–1.66)						125	125	74%
Parrello et al. 1997[80]	Case-control	3.11 (1.54–6.3)						536	755	67%
Corrao et al. 1998	Case-control			1.6 (0.9–3.0)		1.3 (0.6–2.8)		594	594	67%
Calkins et al. 1986[81]	Case-control	0.62 (0.11–3.42)						35	32	42%
Calkins et al. 1986[82]	Case-control	0.57 (0.11–2.88)						35	38	42%
Vcev et al. 2015	Case-control	0.75 (0.30–1.88)						62	42	31%
Cornish et al. 2008	Meta-analysis				1.28 (1.06–1.54)		1.07 (0.702–1.640)	883	74,932	91%
Cornish et al. 2008[83]	Meta-analysis				1.24 (0.999–1.54)					91%
Godet et al. 1995[84]	Meta-analysis		1.29 (0.94–1.77)					851	49,875	82%

Ulcerative Colitis References

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[77] Interaction with smoking notes, higher RR in smokers (2.49).
[78] Monozygotic and dizygotic twins.
[79] Twins studies.
[80] Unclear how the calculation was done.
[81] Hospital controls.
[82] Neighborhood controls.
[83] High quality studies.
[84] Adjusted for smoking.

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Systemic Lupus Erythematosus

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

There have been seven studies published evaluating the effect of hormonal contraceptives on susceptibility to systemic lupus erythematosus (Table 9). A significantly increased risk for development of systemic lupus erythematosus with use of COCs was shown for ever use in two studies (Costenbader 2007, Sanchez-Guerrero 1997), for current use in one study (Bernier 2009) and for past use in one study (Costenbader 2007). None of the studies showed a decreased risk. While no meta-analyses of these studies have been performed, the uniformity of the results implicate COCs as an important risk factor for the subsequent development of systemic lupus erythematosus.

Table 9 – Individual Studies of the Effects of COCs on the Development of Systemic Lupus Erythematosus

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Costenbader et al. 2007[85]	Cohort		1.5 (1.1–2.1)				1.7 (1.2-2.3)	262	238,046	96%
Costenbader et al. 2007[86]	Cohort		1.6 (1.1-2.2)				1.6 (1.1-2.2)	164	102,882	96%
Costenbader et al. 2007[87]	Cohort		2.3 (1.0-5.0)				2.3 (1.1-5.2)	98	107,854	96%
Bernier et al. 2009	Cohort		1.19 (0.98-1.45)		1.54 (1.15-2.07)		1.06 (0.85-1.33)	786	7817	96%
Bernier et al. 2009[88]	Cohort				2.52 (1.14-5.57)			786	7817	96%
Bernier et al. 2009[89]	Cohort				1.45 (1.06-1.99)			786	7817	96%

[85] Pooled RR from the Nurses' Health Study (NHS) and NHS II.
[86] RR from the NHS (data collection through 1976).
[87] RR from NHS II (data collection through 1989).
[88] RR for short term use (starting COCs within ≤3 months).
[89] RR for long term use (starting COCs over 3 months previously with current use ongoing).

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Sanchez-Guerrero et al. 1997	Cohort		1.4 (0.9-2.1)					99	121,546	88%
Sanchez-Guerrero et al. 1997[90]	Cohort		1.9 (1.1-3.3)					58	121,587	88%
Cooper et al. 2002	Case-control			1.5 (0.8–2.7)		1.3 (0.8–2.0)		240	321	92%
Strom et al. 1994	Case-control	0.8 (0.5-1.4)						195	143	73%
Zonana-Nacach et al. 2002[91]	Case-control	2.1 (1.18-3.6)						130	130	61%
Grimes et al. 1985	Case-control			0.5 (0.11-2.3)				109	109	58%

Systemic Lupus Erythematosus References

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Risk of Depression, Mood Disorders, and Suicide

The effects of contraceptive steroid hormones on depression, mood disorders, and suicide have been investigated (Table 10). The largest study of incident depression and use of anti-depressant medication (Skovlund 2016) indicates significantly increased risks for both COCs and POCs for both outcomes. The same group studied for suicide attempts and suicides (Skovlund 2018). Elevated risks were seen, and this was the case for both COCs and POCs. The recent NCHA study (Gregory 2018) showed a similar trend. One study (Keyes 2013) showed a lower risk of depression, but was not measuring clinically diagnosed depression, but rather the presence of depressive symptoms within 7 days prior to the survey. They also found a lower rate of suicide attempts among COC users. Similar findings were seen in 2 studies that also used a questionnaire looking at current COC or POC use (Toffol 2011, Toffol 2012). An analysis of the development of mood disorders found a higher incidence with POCs but a lower incidence with COCs (Svendal 2012). A study of post-partum depression as a reported adverse drug reaction showed higher rates for levonogestrel, etonogestrel and sertraline & drospirenone (Horibe 2018). A study of post-partum DMPA versus copper IUD use showed significant increases in depression scores and major depressive episodes with DMPA (Singata-Madliki, 2016). A retrospective cohort study showed increased risk for antidepressant use in patients who used ethinyl estradiol/etonogestrel (ring), and decreased risk of depression diagnosis with norethindrone-only pills or the levonorgestrel intrauterine system. A small retrospective chart review of the effect of immediate post-partum DMPA did not show significant effects on post-partum depression (Tsai 2009). All the papers, which have broken out the age groups of users, show maximum increased risk for depression, suicide risk, and suicide within 3 months of beginning to use the drugs and tapering off after 6 months, partly due to attenuation of symptoms, partly due to discontinuation due to adverse effects. These risks need to be adequately conveyed in prescribing information and patient-related materials.

[90] Using most stringent definition of systemic lupus erythematosus.

[91] Paper written in Spanish. OR is for use of oral contraceptives for more than one year.

However, little attention has been paid to the effects of blocking the important actions of estradiol and progesterone with progestins during the time of active brain remodeling. Estradiol and progesterone in normal sequence are essential for brain remodeling from ages 15–19 years particularly for myelination, dendritic pruning and establishment of new synaptic connections (Del Rio 2018). Suppressing these with synthetic progestins can have far-reaching, untoward effects. See Griksiene below in Table 10 as well as Del Rio (Del Rio 2018).

Table 10 – Studies of Chemical Contraceptives and Depression, Mood Disorders and Suicides

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	Cases	Controls/Cohort Size
Skovlund 2016 incl /Worley	Prospective Cohort Incident Depression – COCs		1.1[92] (1.08-1.14)			1,061,997
	Incident Depression – POCs		1.2[93] (1.04-1.31)			
	First use of Antidepressants – COCs		1.23[94] (1.22-1.25)			
	First use of Antidepressants – POCs		1.3[95] (1.27-1.40)			
Skovlund 2018 incl /Worley	Prospective Cohort					475,802
	Prospective Cohort Suicide attempts		1.97[96] (1.85-2.10)			
	Suicides		3.08[97] (1.34-7.08)			
Gregory 2018	NCHA survey				146,938	202,759
	Ever Diagnosed with Depression	1.558 (1.506-1.612)				
	Academic performance affected by depression	1.282 (1.245-1.321)				
Keyes 2013	COC reduced depression among women 25-34 years of age.[98] 4 waves of L-Hanes			-1.04[99] (-1.73 - -0.35)	3224	1219
	Suicide attempts			0.38 (0.15-0.97)		
Toffol 2011	Population/choice Cross sectional 30-54 yrs. of age[100]			-0.988[101] (-1.917 – -0.059)		2,310
Toffol 2012	Population-based cross-sectional study[102]			-0.42		8,586

[92] First diagnosis of depression for combined oral contraceptive users.
[93] First diagnosis of depression for all progestin-only method users.
[94] First use of an antidepressant for combined oral contraceptive users.
[95] First use of an antidepressant for all progestin-only method users.
[96] Hazard ratio for suicide attempts; all hormonal contraceptives.
[97] Hazard ratio for suicides; all hormonal contraceptives.
[98] "The presence of depressive symptoms during the past 7 days was assessed in all waves using the Center for Epidemiologic Studies Depression Scale (CES-D)."
[99] β statistic shown.
[100] "The associations between the current use of COCs and the LNG-IUS, and their duration versus mood symptoms [Beck Depression Inventory (BDI)], psychological well-being [(General Health Questionnaire-12 (GHQ-12)] and recent psychiatric diagnoses [(Composite International Diagnostic Interview (CIDI)] were examined among women who participated in the Finnish-population-based Health 2000 study." "Overall, hormonal contraception was well tolerated with few significant effects on psychological well-being."
[101] β statistic shown for the Beck Depression Inventory (BDI). None of the other parameters assessed was statistically significant (including any psychiatric diagnosis, alcohol dependence, major depressive episode or disorder, dysthymic disorder, or anxiety disorder).
[102] Data were collected in the context of the National FINRISK Study Survey, a cross-sectional population-based health survey carried out in Finland every 5 years since 1972. For the purpose of this study, data collected in the years 1997, 2002 and 2007 were analyzed for ages 25–54. OC vs. LNG. inconsistent questions between surveys, BDI, recall bias, etc. "Presence of somatic and psychological symptoms was assessed by asking the participants how often (often, sometimes, not at all) in the previous month they had had one or more out of 13 symptoms." Also administered the Beck Depression Inventory-13. "A negative association between the current use of COCs and Beck Depression Inventory-13 (BDI-13) score was found. Some other negative associations, all characterized by a

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	Cases	Controls/Cohort Size
				(--1.79 - -0.04)[103]		
Svendal 2012[104]	Population-based cross-sectional study				40	458
	POC Use – mood disorder			3.0 (1.1-7.8)		
	COC Use – mood disorder			0.3 (0.1-0.9)		
Horibe 2018	Retrospective[105]				253	6,157,897
	Post-partum depression w/ levonorgestrel			12.5 (8.7-18)		
	Post-partum depression w/ etonogestrel			14.0 (8.5-22.8)		
	Post-partum depression w/ sertraline & drospirenone			5.4 (2.7-10.9)		
Singata-Madliki 2016	Single-blind randomized controlled trial of post-partum DMPA vs. copper IUD			[106]	111[107]	117[108]
Kulkarni 2005[109]	Case-control pilot study COCs vs non-users			p=0.001 depression for all scales[110]	26	32
Roberts 2017	Retrospective cohort study[111]			With Dx of depression[112]	31,506[113]	44,022[114]
	Norethindrone-only pills			0.56 (0.49-0.64)		
	Levonorgestrel intrauterine system			0.65 (0.52–0.82)		
	Etonogestrel subdermal implant			1.01 (0.83–1.22)		
	Ethinyl estradiol/ norgestimate (pill)			0.89 (0.70–1.14)		
	Ethinyl estradiol/norethindrone (pill)			0.82 (0.59–1.12)		
	Ethinyl estradiol/etonogestrel (ring)			1.09 (0.80–1.50)		
Tsai 2010	Retrospective chart review[115]	DMPA	Controls		55	192
	Mean EPDS scores at 6 weeks postpartum	5.02	6.17			

small effect size, were detected between current use of COCs and the BDI items feelings of dissatisfaction, feelings of uselessness, irritability, lost interest in people and lost appetite."

[103] Results for the BDI-13 shown. Other parameters (including BDI-21, low mood last year, anhedonia last year, recent diagnosis of depression and recent other psychiatric diagnosis) did not reach statistical significance.

[104] Women in Australia 20-50 years of age. Evaluated for the occurrence of mood disorders, including major depressive disorder (MDD), minor depression, bipolar disorder, dysthymia, mood disorder due to a general medical condition and substance induced mood disorder.

[105] Data is from the FDA Adverse Event Reporting System (FAERS) database. Reporting Odds Ratios (ROR) are shown.

[106] Beck Depression Inventory (BDI-II) and the Edinburgh Postnatal Depression Scale (EPDS) evaluated. The one-month EPDS depression scores were statistically significantly higher in the DMPA arm compared with the IUD arm (p=0.04). Three-month BDI-II scores were significantly higher in the DMPA arm than in the IUD arm (p=0.002) and, according to the BDI-II but not the EPDS, more women in the DMPA arm had major depression at this time-point (8 vs 2; p=0.05).

[107]111 randomized to DMPA.

[108] 117 randomized to IUDs.

[109] Assessment tools included three depression rating scales: Beck Depression Inventory (BDI), Hamilton Rating Scale for Depression (HAMD) and Montgomery-Asberg Depression Rating Scale (MADRS); also used the Global Assessment of Functioning (GAF) Scale.

[110] ANOVA of GAF, BDI, HAMD &MADR scales all significantly different.

[111]Post-partum depression with hormonal contraception.

[112] Adjusted hazard ratios shown.

[113] Number on hormonal contraceptives.

[114] Number not on hormonal contraceptives.

[115]Depot medroxyprogesterone in the immediate post-partum period and depression. Evaluated the Edinburgh Postnatal Depression Scale (EPDS).

	Study Design	OR Ever Use	RR Ever Use	OR Current Use	Cases	Controls/Cohort Size
Griksiene 2011	Case-control study[116]	[117]			23[118]	20[119]

Depression, Mood Disorders, and Suicide References

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Worly Brett L, Gur TL, and Schaffir J. The relationship between progestin hormonal contraception and depression: a systematic review. *Contraception* 2018; 97:478–489.

Young EA, Kornstein SG, Harvey AT, Wisniewski SR, Barkin J, Fava M, Trivedi MH, and Rush AJ. Influences of Hormone-Based Contraception in Depressive symptoms in Premenopausal Women with Major Depression. *Psychoneuroendocrinology* 2007; 32(7):843–853.

Multiple Sclerosis

Papers were accessed from a PubMed literature review as noted (Williams 2017). Each paper was rated based on the parameters noted in the STROBE statement (von Elm 2007).

[116] Verbal fluency and mental rotation (spatial perception) are affected by progestins w/androgenic or antiandrogenic properties.
[117] Naturally cycling women performed better on verbal fluency task as compared to OC users. Subjects who used the third generation (androgenic) COCs generated significantly fewer words as compared to new generation (anti-androgenic) OC users and non-users. The third generation OC users demonstrated significantly longer RT in MRT task as compared to non-users. The MRT, verbal fluency and mood parameters did not depend on the phase of menstrual cycle.
[118] Women on hormonal contraception.
[119] Control women not on hormonal contraception.

A total of 6 studies (3 cohort studies and 3 case-control studies) were identified which evaluated the impact of COCs on the subsequent development of multiple sclerosis (Table 11). Two studies showed a significantly increased risk for the development of multiple sclerosis with ever use of COCs (Hellwig 2016, Kotzamani 2012) with a similarly increased risk noted in one study for current use or past use (Hellwig 2016). Overall these studies suggest that use of COCs may convey an increased risk for the subsequent development of multiple sclerosis.

Table 11 – Individual Studies of the Effects of COCs on the Development of Multiple Sclerosis

Study	Study Design	OR Ever Use	RR Ever Use	OR Current Use	RR Current Use	OR Past Use	RR Past Use	Cases	Controls	Quality Score
Hernán et al. 2000[120]	Cohort		1.1 (0.9-1.5)		1 (0.6-1.6)		1.2 (0.9-1.5)	313	237,318	90%
Thorogood et al. 1998[121]	Cohort				1.2 (0.7-2.0)		1.3 (0.9-2.0)	114	46,000	75%
Villard-Mackintosh et al. 1993	Cohort		0.8 (0.5-1.4)					63	16,969	65%
Hellwig et al. 2016	Case-control	1.51 (1.12-2.03)		1.47 1.05-2.05		1.55 (1.20-2.00)		400	3804	92%
Kotzamani et al. 2012	Case-control	1.6 (1.1-2.4)						254	314	81%
Alonso et al. 2005[122]	Case-control	0.6 (0.4-1.0)		0.5 (0.3-1.2)		0.6 (0.4-1.0)		106	1001	77%

Multiple Sclerosis References

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Interstitial Cystitis

A case-control study (Konkle 2012) showed significantly higher use of birth control pills in cases versus controls: 88% versus 82%; P = 0.019. Another case-control study showed that use of COCs markedly increased the risk of the disease whether past (OR 4.6, 95% CI 1.74-12.1) or current use (OR 6.9, 95% CI 2.1–22.1). Interstitial cystitis was associated with vulvodynia and sexual dysfunction in a high number of cases (Gardella 2011). Another study showed that use of COCs in patients with interstitial cystitis was associated with a decrease in quality of life (El Khoudary 2009). One meta-analysis (Champaneria 2015) showed that ever use of COCs significantly increased the risk of interstitial cystitis (OR 2.31, 95% CI 1.03–5.16).

Overall, use of COCs appears to be associated with an increased risk for the development of interstitial cystitis.

Interstitial Cystitis References

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[120] NHS I and II cohorts.

[121] Funded by drug companies that make HCs.

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Osteoporotic Bone Fractures

Prescribing information for POCs typically includes a warning regarding the development of osteoporosis. However, the more relevant outcome is fracture risk. Therefore, articles were sought that looked at the effect of COCs and POCs on fracture risk. Data were initially derived from a systematic review of the evidence from observational studies of hormonal contraceptive use for contraception and the risk of fracture in women by Lopez (Lopez 2015). They noted that in 2004, the US Food and Drug Administration added a warning to depot medroxyprogesterone acetate (DMPA) labeling about the potential loss of BMD (FDA 2004), which might limit long-term use. A systematic review of progestin-only methods found an association between DMPA use and loss of bone mineral density (Curtis 2006). Lopez identified 559 records, 524 of which did not meet their inclusion criteria. Thirty-five full-text reports remained, 11 of which were excluded. Of the remaining 24, 10 were secondary articles. That left 14 articles: the 14 studies examined oral contraceptives (N = 12), DMPA (N = 4) and the hormonal IUD (N = 1). Similar search terms to Lopez were used for papers published since 2015 and 2 additional papers were retrieved. The resulting studies are shown in Table 12.

COCs: Three early studies (Cooper 1993, Tuppurainen 1993, Vessey 1998) showed an increase risk of fracture with use of COCs. These studies predominately evaluated pre-menopausal fracture risk. Others that evaluated wrist fracture linked to falling had few cases but showed a trend to decreased risk (O'Neill 1996). One study that evaluated post-menopausal fracture risk based on prior oral contraceptive use (Barad 2005) also found an increased fracture risk. Another study looking at hip fracture risk in elderly women (Michaëlsson 1999) showed a decreased risk but is compromised in that "The exposure time for oral contraceptives may thus maximally have spanned 5 years…" Two studies by Vestergaard (Vestergaard 2006 and Vestergaard 2008) looked at any fracture with OC use and did not show a significant effect when multivariate analyses were performed. However, these studies only looked at use within the past 5 years and did not take into account remote use or cumulative lifetime use. A small cross-sectional study in southern Tasmania (Wei 2011) was stratified by duration of use and showed a reduction in vertebral deformities for 5-10 years of use, but no effect for shorter or longer duration of use and no effect on number of vertebral deformities. A large case-control study which evaluated incident fracture risk with varying numbers of COC prescriptions showed an increased risk for 10+ prescriptions with current use (Meier 2010). A similar study failed to confirm this for most prescription numbers (Kyvernitakis 2017) but this study had fewer subjects reducing its power. A case-control study (Memon 2011) nested in an earlier cohort study (Cooper 1993) failed to show an effect.

Overall the weight of evidence for use of COCs suggests an increased risk of bone fracture with protracted use. The study by Barad (2005) appears to have the largest number of subjects, was a cohort study, and was the only study that evaluated post-menopausal fracture risk with prior use of COCs.

In contrast, virtually all the studies evaluating POCs show an elevated risk (Lanza 2013, Vestergaard 2008b, Meier 2010, Kyvernitakis 2017). This risk appears to increase with duration of use.

Table 12 – Individual Studies of the Effects of Contraceptives on the Development of Osteoporotic Fractures

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Cooper 1993[123]	Cohort	COCs		1.20 (1.08-1.34)		1365	46,000	All fractures
Vessey 1998[124]	Cohort	COCs		1.5 (1.1-2.1)		1308	17,032	First fracture: radius or ulna
Vessey 1998[125]	Cohort	COCs		1.2 (1.1-1.4)				First fracture: all sites

[123] From the Royal College of General Practitioners (RCGP) Oral Contraception Study.
[124] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.
[125] OC use > 97 months vs no use. Recruited age 25 to 39 years; followed to 45 years.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Vessey 1998[126]	Cohort	COCs		2.5 (1.5-4.0)				First fracture: radius or ulna
Vessey 1998[127]	Cohort	COCs		1.3 (1.1-1.5)				First fracture: all sites
Vessey 1998[128]	Cohort	COCs		5.7 (p=0.017)				First fracture: radius or ulna
Vessey 1998[129]	Cohort	COCs		11.2 (p<0.001)				First fracture: all sites
Barad 2005[130]	Cohort	OCs[131]		1.07 (1.01–1.15)		4,674	80,947	First fracture
Barad 2005[132]	Cohort	OCs		1.15 (1.04-1.27)		4,674	80,947	First fracture
Barad 2005[133]	Cohort	OCs		1.09 (0.97–1.23)		4,674	80,947	First fracture
Lanza 2013[134]	Retrospective cohort study	DMPA[135]		1.41 (1.35–1.47)		11,822	312,395	Incident fractures
	Past use[136]	DMPA		1.32 (1.24–1.41)				Incident fractures
	Recent use[137]	DMPA		1.41 (1.31–1.50)				Incident fractures
	Current use[138]	DMPA		1.51 (1.41–1.61)				Incident fractures
Tuppurainen 1993[139]	Case-control	OCs	1.21 (0.93-1.57)			629	13,100	All fractures
Tuppurainen 1993[140]	Case-control	OCs	1.35 (0.88-2.05)			210	13,100	Wrist fractures
O'Neill 1996	Case-control	OCs	0.3 (0.1-0.9)			62	116	Distal forearm fractures only Population controls
O'Neill 1996	Case-control	OCs	0.7 (0.2-2.4)			62	50	Distal forearm fractures only Fall controls
Michaëlsson 1999[141]	Case-control	Any[142]	0.75 (0.59–0.96)			1327	3312	Hip fractures

[126] Interval since use: 73 to 96 months vs no use (radius or ulna). Recruited age 25 to 39 years; followed to 45 years.
[127] < 12 months vs no use (all fractures). Recruited age 25 to 39 years; followed to 45 years.
[128] X^2 trend.
[129] X^2 trend.
[130] Recruited age 50 to 74 years; OC use: any vs none.
[131] The patients were asked about oral contraceptive use, which likely was predominantly COCs but was not broken down with regard to COCs or POCs.
[132] Among women without any postmenopausal hormone treatment, past OC use for 5 years or less.
[133] Among women without any postmenopausal hormone treatment, past OC use for more than 5 years.
[134] They note that, "Although DMPA users experienced more fractures than nonusers, this association may be the result of confounding by a pre-existing higher risk for fractures in women who chose DMPA for contraception." However, this is based on analysis of relatively few fractures prior to DMPA use.
[135] Depot medroxyprogesterone acetate = DMPA.
[136] Active DMPA use based on the interleaving of active 90-day exposures generated by each injection.
[137] Recent exposure is 640 or fewer days after the last active exposure.
[138] Past exposure begins after "recent" exposure (641 or more days after the last active exposure).
[139] Oral contraceptive use for 6+ years.
[140] Oral contraceptive use for 6+ years.
[141] No significant correlation was seen with duration of use, time since last use or time between last use and menopause.
[142] Any type of chemical contraceptive was evaluated, not separated as COCs or POCs.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Vestergaard 2006[143]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<25 years[144]	OCs	0.97 (0.91–1.03)	0.96 (0.92–1.01)	0.92 (0.86–0.98)			Any fracture in the year 2000
	25-49 years	OCs	0.91 (0.82–1.00)	0.90 (0.77–1.05)	0.87 (0.64–1.18)			Any fracture in the year 2000
	50+ years	OCs	0.92 (0.77–1.10)	0.69 (0.45–1.05)	0.62 (0.27–1.41)			Any fracture in the year 2000
Vestergaard 2008a[145]	Case-control	OCs	<0.3 DDD/day	0.3–0.99 DDD/day	1+ DDD/day	64,548	193,641	Any fracture in the year 2000
	<15	OCs	1.02 (0.75–1.37)	1.17 (1.01–1.37)	0.97 (0.85–1.11)			Any fracture in the year 2000
	15.1-17	OCs	1.22 (1.02–1.47)	1.14 (1.00–1.30)	1.04 (0.90–1.19)			Any fracture in the year 2000
	17.1-19	OCs	0.97 (0.87–1.09)	0.93 (0.84–1.02)	1.02 (0.89–1.18)			Any fracture in the year 2000
	>19	OCs	0.99 (0.93–1.05)	1.00 (0.93–1.08)	0.88 (0.78–0.99)			Any fracture in the year 2000
Vestergaard 2008b[146]	Case-control	DMPA	1.44 (1.01–2.06)			64,548	193,641	Any fracture in the year 2000 DMPA use
Wei 2011[147]	Cross-sectional		<5 years of use	5-10 years of use	>10 years of use		491	
		OCs	0.85 (0.45–1.58)	0.45 (0.21–0.93)	0.75 (0.36–1.54)			Presence of vertebral deformity
		OCs	0.96 (0.62–1.48)	0.63 (0.37–1.07)	0.94 (0.56–1.56)			Number of vertebral deformities
Meier 2010[148]	Case-control		Current Use	Past Use		17,527	70,130	Incident fracture
	1-2 DMPA Scripts	DMPA	1.18 (0.93–1.49)	1.17 (1.07–1.29)				Incident fracture
	3-9 DMPA scripts	DMPA	1.36 (1.15–1.60)	1.23 (1.11–1.36)				Incident fracture
	10+ DMPA scripts	DMPA	1.54 (1.33–1.78)	1.30 (1.09 – 1.55)				Incident fracture
	1-2 COC Scripts	COCs	1.01 (0.87–1.18)	1.00 (0.95–1.07)				Incident fracture
	3-9 COC scripts	COCs	1.01 (0.94 – 1.09)	0.99 (0.94 – 1.04)				Incident fracture
	10+ COC scripts	COCs	1.09 (1.03–1.16)	1.03 (0.97–1.10)				Incident fracture

[143] "The exposure time for oral contraceptives may thus maximally have spanned 5 years (from January 1, 1996, to December 31, 2000)." This and the other Vestergaard study are not useful as they do not take into account remote use or cumulative lifetime use. ORs shown.

[144] Defined daily dosages = DDD.

[145] Similar to Vestergaard 2006; only looked at use within the past 5 years. A younger group examined here. ORs shown.

[146] Similar to Vestergaard 2006; only looked at use within the past 5 years. DMPA examined here. ORs shown.

[147] Small cross-sectional study. ORs shown.

[148] Females aged 20–44 years with an incident fracture diagnosis between 1995 and 2008.

Study	Study Design	Intervention	OR	RR		Cases	Controls or Cohort Size	Outcome
Memon 2011[149]	Case-control	COCs	1.05 (0.86-1.29)			651	1302	Any fracture
Kyvernitakis 2017[150]	Case-control		OR Current Use	OR Past Use		4189	4189	First-time fracture diagnosis
	1-2 DMPA scripts	DMPA	0.97 (0.51–1.86)	0.96 (0.73–1.26)				
	3-9 DMPA scripts	DMPA	2.41 (1.42–4.08)	1.14 (0.86–1.51)				
	10+ DMPA scripts	DMPA	1.46 (0.96–2.23)	1.55 (1.07–2.27)				
	1-2 COC scripts	COCs	0.98 (0.73–1.31)	0.90 (0.77–1.05)				
	3-9 COC scripts	COCs	1.39 (1.12–1.73)	0.90 (0.78–1.03)				
	10+ COC scripts	COCs	1.07 (0.88–1.30)	1.04 (0.90–1.21)				

Osteoporotic Fracture References

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Impact of Contraceptives on Body Mass

Weight gain is a common complaint among contraceptive users but whether use of contraceptives is causally related remains undefined. Progestin-only contraceptives are most commonly associated with weight gain complaints and discontinuation. A recent Cochrane review (Gallo et al. 2014) examined the effect of combined oral contraceptives on weight gain and concluded existing data does not support a causal relationship. A second review of progestin-only contraceptives on weight gain (Lopez et al. 2016) found most studies of low to moderate quality but did conclude weight gain of up to 2kg (4.4 lbs) within the first year of use with continued increases thereafter. The authors advised appropriate counselling on expected weight changes to minimize discontinuation due to perceived weight gain.

The attached table (Table 13) summarizes studies of 1 year or longer that examined weight and body mass changes in contraceptive users in comparison to non-hormonal contraceptives or no method. Several additional studies compare various contraceptives for their effect on weight or body composition, but these do not directly address our focus.

The strongest data appear to be the deleterious effects of levonorgestrel-releasing IUDs on percent lean and fat body mass. Total body weight change does not appear different between groups and several large studies have shown no significant differences. However, a significant increase in % fat mass with a corresponding decrease in % lean body mass was observed in both studies where these were measured. A similar effect was seen from oral desogestrel in a single study.

Thus, while limited to date, data suggest that use of progestin-only contraceptives may have deleterious effects on % fat and % lean body mass with no significant overall effect on total body weight.

A review of current Mirena labeling makes no mention of changes in lean or fat body mass composition.

Retrospective, but not more recent, prospective studies also show DMPA use is associated with significant gains in weight. The data appear too mixed to draw firm conclusions.

Table 13 – Effect of Chemical Contraceptives on Weight Gain

Study	Design	Comparison	N	Time	Weight change (Kg)	Fat mass change	Lean mass change	Comments
Pantoja 2010	Retrospec.	DMPA 150 vs CuIUC	758	1yr	1.76 vs-0.42*			Largest differences noted in normal and overweight BMI subgroups, minimal differences in obese BMI subgroup
				2yr	3.1 vs 0.4*			
				3yr	3.9 vs 0.8*			

Study	Design	Comparison	N	Time	Weight change (Kg)	Fat mass change	Lean mass change	Comments
Modesto 2015	Retrospec.	DMPA150 vs CuIUC	1277	1yr	1.3 vs 0.2*			
				4yr	3.5 vs 1.9*			Adjusted for years of school & # children. 20% loss @4yrs 84% @ 10yr.
				10yr	6.6 vs 4.9*			
Taneepanichuskul 1998	Retrospec.	DMPA 150 vs CuIUC	100	10yr	10.9 vs 11.2			Included women 37-50 years (no younger women)
Vickery 2013	Prospec.	DMPA 150 vs CuIUC	167	1yr	2.2 vs 0.16			CHOICE study subgroup
Dal'Ava 2014	Prospec.	DMPA 150 vs CuIUC	110	1yr	1.9vs 1.1	1.6 vs -0.9 (Kg)	0.3 vs 1.2 (kg)	Paired by age (+/-2yr) & weight (+/-2kg)
Dos Santos 2014	Prospec.	DMPA 150 vs CuIUC	71	1yr	1.4 vs 0.3	1.57 vs 0.52 (kg)	(0.31) vs (0.26) (kg)	Matched by age & BMI
								()= negative value

Studies comparing LNG IUC to non-hormonal contraceptive

Study	Design	Comparison	N	Time	Weight change (Kg)	Total body fat	Lean body mass	
Dal'Ava 2012	Prospec.	LNG-IUC vs non-hormonal IUC	76	1yr	2.9 vs 1.4	2.5% vs -1.3%*	(1.4%) vs 1.0%*	Paired by age & BMI
Napolitano 2015	Prospec.	LNG IUC vs no method	60	1yr	0.6 vs (0.2)	1.1% vs (0.5%)*	(1.1%) vs 0.5*	
Vickery 2013	Prospec.	LNG-IUC vs Cu IUC	230	1yr	1.03 vs 0.16	nd	nd	
Modesto 2015	Retrospec.	LNG-IUC vs CuIUC	1204	1yr	0.7 vs 0.2	nd	nd	
				4yr	2.7 vs1.9			
				10yr	4.0 vs 4.9			

Studies comparing progestin-only COCs to non-hormonal

Study	Design	Comparison	N	Time	Weight change (Kg)	Total body fat	Lean body mass	
Napolitano 2015	Prospec.	Desogestrel 75ug vs no hormonal	68	1yr	0.3 vs -0.2	1.1% vs -0.5%*	(2.8%) vs 0.5%*	

Studies comparing combined COCs to non-hormonal

None found-

Abstract from 2014 Cochrane review of combined oral contraceptives on weight gain:
"We found 49 trials that met our inclusion criteria. The trials included 85 weight change comparisons for 52 distinct contraceptive pairs (or placebos). *The four trials with a placebo or no intervention group did not find evidence supporting a causal association* between combination oral contraceptives or a combination skin patch and weight change. Most comparisons of different combination contraceptives showed no substantial difference in weight. In addition, discontinuation of combination contraceptives because of weight change did not differ between groups where this was studied.
Gallo MF, Lopez LM, Grimes DA, Carayon F, Schulz KF, Helmerhorst FM. Combination contraceptives: effects on weight. Cochrane Database of Systematic Reviews 2014, Issue 1. Art. No.: CD003987.

* Significant difference ($p<0.05$).

Impact of Contraceptives on Body Mass References

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Urogenital Effects of Contraceptives

In addition to cervical cancer and interstitial cystitis, noted above, there are other adverse urogenital effects of COCs that should be communicated to patients. These include bacteriuria (Zahran 1976; calculated OR 3.57), urinary tract infection (Engel 1979: 27–50% incidence), bladder trabeculation (Zahran 1976; calculated OR 11.7), recurrent vulvovaginal candidiasis (Spinollo 1995, Yusuf 2007; OR 2.08), vaginal dryness (Lee 2017), vulvar vestibulitis (Champaneria 2016: OR 2.1 95 % CI 1.26–3.49; also noted in Lee 2017), and Female Sexual Dysfunction (FSD) (Lee 2017). FSD appears related to OC-induced dyspareunia, reduced sexual desire and libido (Lee 2017). This risk is increased if COCs are used in adolescents and the duration of OC use is at least 2 years (Lee 2017), although some newer COCs containing drospirenone 3 mg plus EE 30 mg and gestodene 75 mg plus EE 20 mg appear to have a reduction in these risks (Lee 2017).

These urogenital risks, especially FSD where there is substantial literature, should be referenced in prescribing information and patient pamphlets.

Urogenital Effects References

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Venous Thromboembolism and Contraceptives

The current language on the black box warning of certain contraceptives regarding risk of cardiovascular events clearly misleads women about the real risks of these drugs. It says: WARNING: CIGARETTE SMOKING AND SERIOUS CARDIOVASCULAR EVENTS. A study (Gomer 2009) conducted among 300 women concluded "that most of them believe that certain risks are only associated with being over 35 years of age and/or smoking." Instead, the label should clearly state that anyone taking the medications without good knowledge of the risk factors could experience a potentially life-threatening cardiovascular event and should discuss the risks with a medical provider.

The incidence of venous thromboembolism (VTE) for healthy women can significantly increase with the use of hormonal contraceptives, even women under 35 and not-smoking. In a 2012 article about birth control side effects, Dr. Rebecca Peck (Peck R 2012) reports that "Oral contraceptives are associated with a three to five times higher risk of VTE (Van Hylckama VA 2009)." Third and fourth generation combined hormonal contraceptives (CHC) have been found to put women at an even much higher risk, leading to major lawsuits against some manufacturers and changes in regulations in several countries. In his opinion published in Drug Safety, Dr. Lidegaard, the author of several studies on the subject, states: "Of 14 studies specifically assessing the risk in users of CHC with desogestrel or gestodene, 13 found a higher risk with use of these products when compared to the use of CHC with levonorgestrel" (Lidegaard 2014). Drospirenone, the progestin contained in Yaz and Jasmine, also increases the risk of VTE over levonorgestrel by a factor of 1.5 to 2.8. "The relative risk [of Drospirenone was 6.3 as compared with nonusers in both the large Dutch (Van Hylckama 2009) and Danish (Lidegaard 2011) study." The author comments that "the studies demonstrating risk differences between CHC with different progestins are generally methodologically more transparent and more robust than those demonstrating no difference, especially concerning exclusion of women with predispositions for VTE." Another large study published in 2015 (Vinogradova 2015) reviewed 10,552 cases of VTE reported between 2001 and 2013 in the UK and found similar elevated risks of VTE with these CHC: "Corresponding risks associated with current exposure to desogestrel (4.28, 3.66 to 5.01), gestodene (3.64, 3.00 to 4.43), drospirenone (4.12, 3.43 to 4.96), and cyproterone (4.27, 3.57 to 5.11) were significantly higher than those for second generation contraceptives levonorgestrel (2.38, 2.18 to 2.59)." Note that the odds ratios were "adjusted for smoking status, alcohol consumption, ethnic group, body mass index, comorbidities, and other contraceptive drugs."

Most importantly, the risk levels are multiplied if women have other risk factors. For instance, women who have the genetic blood condition known as Factor V Leiden could have a risk as high as 18 per 10,000 woman-years. If these women stay on the product for 10 years, their risks could be 250 per 10,000 woman-years, or 2.5% as risks increase with aging (Lidegaard 2014).

Dr. Lidegaard concludes: "Therefore, women with known risk factors of VTE are advised to be reluctant to use CHC. The relative risk of VTE with different dispositions is as follows: previous thrombosis: > 50 (Le Moigne2013), genetic abnormalities such as factor V Leiden mutation (heterozygous): 6, deficiency of protein C: 10, of protein S: 10, of antithrombin: 25, and of prothrombin 20210A: 3 (Phillippe 2014). Pregnancy with delivery on average: 8, adiposity: 2–3 and immobilization 2–5 depending on how long time you are immobilized. Family disposition (first-degree relatives with VTE before their 50th year) doubles the risk of VTE. Women with such dispositions are generally recommended to use progestin-only contraception, which does not increase the risk of VTE except perhaps for medroxyprogesterone depots. A genetic screening should until further also be restricted to women with a family disposition" (Lidegaard 2014).

In a 2018 systematic review (Keenan 2018) of the most evidenced-based articles from the 1960s to 2018 comparing users of COCs to nonusers, with a confirmed diagnosis of VTE, and including more than 17 million woman-years of observation, women on HC increase their risk by 3- to 9-fold. However, the first year of use has the highest risk for clot formation, and if a woman is younger than 30, her risk is increased 13-fold in the first year. Obesity can increase the risk of being on hormonal contraception, about doubling the risk compared to a woman of normal weight on the pill. It is not considered cost-effective to check for thrombophilia, a genetic disposition to form blood clots, but for those with thrombophilia, the risk can be as high as 62-fold in the first year.

This systematic review of the literature concludes that 136–260 women die from VTE a year in the United States from hormonal contraception. Combined with the added risk of stroke and heart attack from the COCs, 300–400 women die each year in the United States simply due to their choice of using HC for family planning (Keenan 2018). To give some perspective, meningitis killed 45 people (of all ages) in 2017: most US States mandate meningitis vaccination for college and university students.

A summary of studies is shown in Table 14.

Table 14 – Relative Risk of Venous Thromboembolism in Current Users of Different Combined Hormonal Contraceptives as Compared with Nonusers Unless Otherwise Specified

Study	Data Sampling Period	VTE (number)	CHCs with levonorgestrel RR (95% CI)	CHCs with desogestrel/gestodene RR (95% CI)	CHCs with drospirenone RR (95% CI)
Blomenkamp 1995	1988 - 1992	126	3.8 (1.7 - 8.4)	8.7 (3.9 - 19.3)	-
WHO 1995a, 1995b	1989 - 1993	433	3.6 (2.5 - 5.1)	7.4 (4.2 - 12.9)	-
Jick 1995	1991 - 1994	80	1 (reference)	1.8 (1.0 - 3.2)	-
Spitzer 1996	1991 - 1995	471	3.7 (2.2 - 6.2)	6.7 (3.4 - 13.0)	-
Lewis 1999	1993 - 1995	502	2.9 (1.9 - 4.2)	2.3 (1.5 - 3.5)	-
Farmer 1997	1991 - 1995	85	3.1‡ (2.1 - 4.5)	5.0‡ (3.7 - 6.5)	-
Todd 1999	1992 - 1997	99	1 (reference)	1.4 (0.7 - 2.8)	-
Bloemenkamp 1999	1994 - 1998	185	3.7 (1.9 - 7.2)	5.6 (not given)	-
Parkin 2000	1990 - 1998	26	5.1 (1.2 - 21.4)	14.9 (3.5 - 64.3)	-
Lidegaard 2002	1994 - 1998	987	2.9 (2.2 - 3.8)	4.0 (3.2 - 4.9)	-
Dinger 2007	2000 - 2004	118	1 (reference)	1.3 (NA)	1.0 (0.6 - 1.8)
Vlieg 2009	1999 - 2004	1524	3.6 (2.9 - 4.6)	7.3 (5.3 - 10.0)/5.6 (3.7 - 8.4)	6.3 (2.9 - 13.7)
Lidegaard 2009	1995 - 2005	4213	2.0 (1.8 - 2.3)	3.6 (3.3 - 3.8)	4.0 (3.3 - 4.9)
Dinger 2010	2002 - 2008	680	1 (reference)	NA	1.0 (0.6 - 1.8)
Parkin 2011	2002 - 2009	61	1 (reference)	NA	2.7 (1.5 - 4.7)
Jick 2011	2002 - 2008	186	1 (reference)	NA	2.8 (2.1 - 3.8)
Lidegaard 2011	2001 - 2009	4246	2.2 (1.7 - 2.8)	4.2 (3.6 - 4.9)	4.5 (3.9 - 5.1)
Confirmed only	2001 - 2009	2707	2.9 (2.2 - 3.8)	6.8 (5.7 - 8.1)	6.3 (5.4 - 7.5)
FDA Kaiser 2011	2001 - 2007	625	1 (reference)	NA	1.5 (1.2 - 1.9)
Gronich 2011	2002 - 2008	518	1 (reference)	1.4 (0.9 - 2.1)	1.7 (1.0 - 2.7)
Lidegaard 2012	2001 - 2010	5287	3.2 (2.7 - 3.8)	6.5 (4.7 - 8.9)*	NA
Dinger 2014	2005 - 2010	162	1 (reference)	NA	0.8 (0.5 - 1.6)

‡ Absolute risk per 10,000 years.
* Vaginal ring with the third-generation progestin etonogestrel.

Venous Thromboembolism References

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Atherosclerosis and Cardiovascular Events

Noting that previous studies had demonstrated women on oral contraceptives (OC) faced a fourfold increased risk of heart attack (Hennekens 1977; Vessey 1976; Beral 1976), researchers in 1982 set out to understand the pathogenesis of vascular disease related to COCs. They found that combination oral contraceptives (COC) caused "greater cell proliferation and incorporation…in both human arterial smooth muscle cells and dermal fibroblasts." Smooth muscle cell proliferation is an integral feature of all atherosclerotic lesions (Bagdade 1982).

In 2007, a presentation at the American Heart Association meeting described a study of 1,301 Belgian women, which showed that women had a 20 to 30 percent increase of plaque for every decade on COCs (Rietzschel 2007). They performed a multivariate adjustment for age, smoking, blood pressure, lipids, obesity, diabetes, physical activity, fruit, vegetable and alcohol intake, educational level and drug therapy (lipid-lowering, antihypertensive, aspirin). Use of OC was associated with a significant increase in carotid or femoral unilateral plaque (OR per 10 years of OC exposure were: carotid plaque 1.17 (1.00 –1.33) and femoral plaque 1.28 (1.10 –1.47). When evaluating the prevalence of bilateral disease (involvement of right and left carotid/femoral artery) as a more stringent phenotype of atherosclerosis, the OR per 10 years OC exposure were 1.42 (1.03–1.84) for carotid plaque and 1.34 (1.05–1.63) for femoral plaque.

They later noted that active OC users had elevated C-reactive protein levels, three times higher than non-users. C-reactive protein is a biomarker for many inflammation-related arterial (and autoimmune) diseases, which was recently the subject of another presentation (Rietzschel 2018). After a similar multivariate analysis, they found the hs-CRP levels were (adjusted geometric means [95% CI]) were: non-users (NoH) 1.0 [0.9 –1.1]; hormone replacement therapy (HRT) users 1.2 [1.1–1.5] and OC users 3.3 [3.0 –3.6]; (OC vs NoH: $p<0.001$; HRT vs NoH: $p<0.05$).

This group also evaluated the carotid and femoral pulse wave velocity (PWV), a measure of arterial stiffness (Rietzschel 2008). They found the average PWV among non-users was 6.6 m/sec, while the average among current OC users was 6.75 m/sec. The blood pressure (BP) of current OC users was also significantly higher (systolic BP (+4.4 ± 0.9 mmHg; $p < 0.001$), diastolic BP (+2.3 ± 0.6 mmHg; $p < 0.001$)). They noted that duration of OC use is a significant determinant of PWV, even after adjustment for age, BP, lipid levels, body size, heart rate, drug therapy (lipid-lowering, antihypertensive), glycemic status and smoking: $F = 6.1$; $p = 0.013$. Per 10 years of OC exposure PWV increased by 0.1 m/s (0.02– 0.18; $p = 0.013$). They concluded that current OC use is associated with increased PWV because OC's increase blood pressure, while long-term use is an independent determinant of PWV, increasing PWV by 0.10 m/s per 10 years exposure (probably through structural remodelling of the vessels). These findings were supported by an evaluation of large artery stiffness in the ENIGMA study (Hickson 2011) although other smaller studies have shown conflicting data (Yu 2014, Priest 2018).

A study of homocysteine and nitric oxide levels compared 50 healthy women with normal menstrual cycles as a control group and 50 healthy women receiving oral contraceptive pills for at least three menstrual cycles (Fallah 2012). They noted that after 3 months of treatment, homocysteine levels were significantly increased ($P = 0.027$), and there was a significant and considerable decrease ($P = 0.048$) in NO concentration of oral contraceptive pill (OCP) consumers. Another study evaluated the effect of COCs on homocysteine and C-reactive protein levels in women (Norouzi 2011). This observational cross-sectional analysis included 90 healthy, non-obese women (mean age 25 years). Forty-five healthy women on OCP and 45 healthy controls were studied. COC users had a minimum of 3 cycles on COCs. The results showed that the homocysteine (13.268±3.475 vs. 7.288±2.621 µmol/L) and CRP (5863.0±1349.5 vs. 1138.3±691.12 ng/ml) levels were significantly higher in women receiving OCP in comparison with the control group ($p=0.027$ and $p<0.001$, respectively). Similarly, a cross-sectional study, in 2011-2012, evaluated 60 healthy premenopausal women (30 cases of COC consumers and 30 controls as nonconsumers), aged between 25 and 45 years who were current users for at least a 3-year period. They evaluated brachial artery endothelial function (using flow-mediated dilatation (FMD)) and common carotid artery intima–media thickness (Heidarzadeh 2014). They noted that there was a significant FMD% difference between 2 groups of cases and controls: 11 ± 3.53 versus 15.80 ± 9.22 ($P = 0.01$). In addition, a significant mean CCA-IMT thickness difference was detected: 0.53 ± 0.07 versus 0.44 ± 0.08 ($P = 0.00$). Although these results were not significant after multiple regression analysis, the authors noted that their results were in favor of early atherosclerotic changes in prolonged users of COCs.

The Danish Heart Association released the results of a 15-year historic cohort study looking at thrombotic stroke and myocardial infarction, which observed over 1.6 million women. The results demonstrated that women taking COCs with ethinyl estradiol at a dose of 20 µg had a risk of arterial thrombosis that was 0.9 to 1.7 times higher than non-users, while those taking a dose of 30 to 40 µg had a 1.3 to 2.3 higher risk (Lidegaard 2012). The risk of thrombotic stroke appeared to be independent of duration of use, while the risk for myocardial infarction increased with duration of use (Table 15).

Together, these studies suggest that protracted use of COCs can induce atherosclerotic changes independent of any pro-thrombotic effect. These changes may contribute to the increase in thrombotic stroke and myocardial infarction seen in COC users.

Table 15 – Relative Risk of Thrombotic Stroke and Myocardial Infarction among Users of Selected Types of Combined Oral Contraception with Ethinyl Estradiol at a Dose of 30 to 40 µg, as Compared with Nonusers, According to Duration of Use (from Lidegaard 2012).

		Thrombotic Stroke		Myocardial infarction	
Duration of use	No. of person-yrs.	No. of events	Relative Risk (95% CI)	No. of events	Relative Risk (95% CI)
<1 year	987,564	213	1.90 (1.64–2.20)	86	1.85 (1.48–2.31)
1-4 years	992,825	194	1.55 (1.33–1.80)	108	1.99 (1.63–2.43)
>4 years	399,461	173	1.93 (1.65–2.26)	91	2.11 (1.70–2.62)

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Conclusion

Hormonal agents have a variety of effects on various organs and organ systems which may result in a deleterious impact on women's health. The data reviewed above reflect a vast body of information which has come to light since the introduction of these agents as contraceptives over 50 years ago. While the information for patients and prescribers currently reflects many of the known side effects, others have come to light which are not adequately represented in the current prescribing information. These should be added and made obvious to patients. In one instance, that of venous thromboembolism, while the warning information is present, it is phrased in a misleading manner which misleads the patients into drawing the incorrect conclusion regarding the risks. In addition, one agent (DMPA) appears to convey a specific risk for HIV transmission which is not shared by other agents. DMPA should be

considered for revoking of marketing authorization and removed from the market. The risks of depression, mood disorders, and suicide have not been adequately emphasized.

We further encourage the Agency to require the manufacturers of these agents to widely publicize these additional risks. Many millions of women are currently receiving COCs and POCs. Many millions more have been exposed to these agents at some point in their lives. They should receive updated information regarding risks which have not been conveyed, or not adequately conveyed, in the past. All women who have been exposed to COCs or POCs should be informed so that they can take this information into account as they may encounter some of these adverse effects in some cases many years after cessation of use.

Environmental Impact

Based on data from the Guttmacher Institute, a conservative estimate of 11 million women aged 15-44 in the US take some form of hormonal contraceptive each day[151]. A 2015 study reports that about 21 percent of women of reproductive years are using some form of hormonal contraceptive, which equates to about 13 million women (Daniels 2015). This has resulted in a significant increase in the release of synthetic progestagens (such as levonorgestrel) and synthetic estrogens (such as ethinylestradiol [EE2]) into the aquatic environment via wastewater treatment plant discharges (Besse 2009, King 2016). EE2 is metabolized in the liver undergoing first pass metabolism, but ~6% of the administered dose appears as untransformed EE2 in the urine and ~9% in the feces (Stanczyk 2013). As noted by King (King 2016), even at low concentrations, these compounds can act as potent endocrine disruptors, affecting the growth, development, and reproduction of exposed aquatic organisms (Tyler 1998, Larsson 1999). EE2 is one of the most studied synthetic hormones in aquatic environments, for which assessments of environmental concentrations and the quantification of endocrine-related effects have been documented in a range of aquatic species (Purdom 1994, Jobling 1998, Kirby 2004, Jobling 2006). In fact, the numerous studies on the effects of EE2 on aquatic organisms have led to the derivation of a reliable predicted no-effect concentration of 0.1 ng/L for EE2 (Caldwell 2012).

In 1993, the first publication appeared which brought attention to the issue of synthetic chemicals mimicking natural estrogen in the environment (Sharpe 1993). The study pointed to environmental pollutants, which were having a deleterious effect on male fetuses in utero – endocrine disruptors like polychlorinated biphenyls, detergents, dioxins, and hormonal contraceptives. In 1995, another paper (Sumpter 1995) noted that male fish in 28 rivers across Britain were being "feminized" by pollutants. In 2002, a paper was published that focused specifically on the effects of endocrine-disrupting chemicals in the environment (Jobling 2002). They demonstrated reduced fertility in fish populations in areas downstream of effluent from sewage plants located along tributaries of the Thames River. In 2007, the results of a seven-year Canadian lake study were published which examined the effects of EE2 (Kidd 2007). The researchers released a quantity of EE2 equivalent to what would come into the waterways via sewage from a city of 200,000 people. They witnessed an immediate feminization and transgendering of male fish, which resulted in the "near extinction" of the fathead minnow population (Kidd 2007). Although the minnow populations neared extinction, they rebounded as soon as the researchers stopped adding EE2 to the lake. A 2006 study from the United States Geological Survey on smallmouth bass in the Shenandoah and Monocacy Rivers found that more than 80-percent of all the male bass living in these waterways were growing eggs in their testes[152].

A study was carried out of fish populations relative to the sewage treatment plants of three major Colorado cities: Denver, Boulder, and Colorado Springs (Woodling 2006). At each municipality, they set up a location just upstream from where the effluent was released, and another just downstream. The fish in the upstream locations enjoyed a balanced 1:1 female-to-male sex ratio. Downstream there were five female fish for every one male, and twenty percent of the reduced male population demonstrated intersex characteristics, such as eggs in their testes and the presence of vitellogenin, an egg yolk protein normally found only in fertile females. The consequences also appeared to ascend up the food chain in a measurable way, specifically with the feminization of trout, mink frogs and green frogs (Parke 2009). Both the predicted and the measured concentrations of EE2 in the US, including effluent of waste water treatment plants, surface water, or ground water, exceeds the predicted no-effect concentrations on fish populations (Kostich 2013).

Environmental factors have been implicated in declining fertility rates (Skakkebaek 2016). A 2017 study out of Hebrew University and Mount Sinai Medical School found that sperm counts in human men have dropped by more than 50 percent since 1973 (Levine 2017). While it has been noted that environmental exposure to individual steroidal estrogens, as well as their mixtures, are unlikely to dramatically affect endocrine signaling in humans, it is not clear whether more subtle effects are possible (Kostich 2013). More recently, environmental effects of levonorgestrel have been postulated (King 2016) but there is less hard data.

There is a clear effect of environmental EE2 on fish populations as well as species higher in the food chain such as frogs. An effect on humans is also possible.

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[151] https://www.guttmacher.org/fact-sheet/contraceptive-use-united-states.

[152] https://dep.wv.gov/WWE/watershed/wqmonitoring/Documents/Potomac-Intersex/USGS_FishHealthReproductiveIssuesPotomac_2006.pdf.

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Economic Impact

For the diseases noted below, in some cases we have calculated the estimated economic impact taking into account those who are currently using COCs and those who have ever used COCs. According to the CDC[153] 15.9% of women aged 15–44 in the US use "the pill." There are 61 million US women of reproductive age (15–44)[154]. This yields 9,699,000 women in the USA currently on COCs.

[153] https://www.cdc.gov/nchs/fastats/contraceptive.htm.
[154] https://www.cdc.gov/nchs/data/nhsr/nhsr086.pdf.

Note that this is a low estimate as it does not include women using intravaginal and transdermal formulations and is lower than the estimate by Daniels (Daniels 2015).

According to the National Survey of Family Growth[155], 79.3% of women surveyed from 2011–2015 have ever used "the pill." This is down from 81.9% in the 2006-2010 survey and 82.3% in the 2002 survey. The lower number for "ever use" of 79.3% is used in subsequent calculations. According to the 2010 census (Howden 2011), there were 156,964,212 women in the US, of whom 24% were under 18 years of age. Thus, there were 119,292,801 women 18 years of age or older. This implies that 119,292,801 x 0.793 = 94,599,191 women in the USA have ever used the pill. As noted above, this does not include women using intravaginal and transdermal formulations.

The numbers 9,699,000 for current use and 94,599,191 for ever use of COCs were used in some of these calculations. In other cases, the census data for specific age groups was used if they were the groups most likely to be impacted by current or recent use of COCs.

For progesterone-only contraceptives (POCs), the National Survey of Family Growth[156], notes that 25.4% of women aged 15–44 in 2011–2015 have ever used "3-month injectable (Depo-Provera™)." This is up from 23.2% in 2006–2010 and 16.8% in 2002. For a conservative estimate, we will use the lowest of these numbers (16.8% or 20,041,191 women) who have ever used POCs. This would not include POCs administered by other routes and is thus a conservative estimate.

HIV Costs

According to the CDC[157], an estimated 255,900 women were living with HIV at the end of 2014. Of these it is estimated 87% were via sexual contact (this proportion was relatively stable from 2011–2016; CDC HIV Surveillance Table 1a). Annual medical cost estimates for HIV-infected persons, adjusted for age, sex, race/ethnicity, and transmission risk group, were from the HIV Research Network (range $1,854–$4,545/month) and for HIV-uninfected persons were from the Medical Expenditure Panel Survey (range $73–$628/month) (Schackman 2015). Using this information along with the prevalence of DMPA use of 16.8%, this suggests an annual cost of treatment for HIV infection due to DMPA use of ~$157-573 million (Table 16).

Table 16 – Estimated Economic Impact of DMPA due to Increased Prevalence of HIV Infection

Women with HIV	255,900
Sexual transmission	87%
Cases due to sexual transmission	222,633
Ever use of DMPA	16.80%
Women with HIV with DMPA use	37,402
RR of HIV with DMPA use	1.4
Adjusted estimate →	26,716
Excess cases →	10,686
Highest estimated individual annual costs →	$53,664
Lowest estimated individual annual costs →	$14,712
Highest estimated total annual costs →	$573,474,111
Lowest estimated total annual costs →	$157,218,081

Breast Cancer

A recent study in the US (Blumen 2016) notes, "The average costs per patient allowed by the insurance company in the year after diagnosis were $60,637, $82,121, $129,387, and $134,682 for disease stage 0, I/II, III, and IV, respectively. The average costs allowed per patient in the 24 months after the index diagnosis were $71,909, $97,066, $159,442, and $182,655 for disease stage 0, I/II, III, and IV, respectively." For all patients, they note that the average cost for the first 12 months following diagnosis is $85,772, and for the second 12 months is $22,127 with a total of $103,735 for the 24 months following diagnosis. For these calculations we will use the first-year costs to estimate costs for incident cases among current users of COCs and will use the second-year cost to approximate the average annual cost of care for a patient diagnosed with breast cancer. According to the NIH SEER statistics[158], the incidence of breast cancer is 126.0 per 100,000 person-years. Approximately 12.4 percent of women will be diagnosed with female

[155] https://www.cdc.gov/nchs/nsfg/key_statistics/c.htm#everused.
[156] https://www.cdc.gov/nchs/nsfg/key_statistics/c.htm#everused.
[157] https://www.cdc.gov/hiv/group/gender/women/index.html.
[158] https://seer.cancer.gov/statfacts/html/breast.html.

breast cancer at some point during their lifetime. According to the best epidemiology studies noted in Table 3 (Mørch 2017; Heikkinen 2016, Lund 2007), and the best meta-analysis in Table 5 (Kahlenborn 2006) the relative risk of ever use of COCs for the development of breast cancer is 1.19–1.37. Based on this information, the estimated increase in cost from use of COCs due to incident cases of breast cancer is between $199 million and $387 million (Table 17).

Table 17 – Estimated Economic Impact of COCs due to Increased Incidence of Breast Cancer

Women of reproductive age	Number on the pill	Incidence		
61,000,000	9,699,000	0.00126		
Estimated women on the pill at risk →		12,221		
Adjusted estimate of cases →		14,543	1.19	Low RR
Adjusted estimate of cases →		16,742	1.37	High RR
Excess cases →		2,322	Low RR	
Excess cases →		4,522	High RR	
Annual cost per patient of breast cancer →		$85,772		
Estimated annual costs →		$199,157,489	Low RR	
Estimated annual costs →		$387,833,005	High RR	

To evaluate the impact of "ever use" of COCs on prevalent breast cancer, we noted that the best meta-analysis (Kahlenborn 2006) showed a 1.19 odds ratio of breast cancer with COCs. According to the SEER statistics, there are currently 3,418,124 prevalent cases of breast cancer in the USA. The estimated increase in cost from treatment of the excess cases of breast cancer is estimated to be ~$9.6 billion annually (Table 18).

Table 18 – Estimated Economic Impact of COCs due to Increased Prevalence of Breast Cancer

Prevalent cases of breast cancer	Ever use of COCs	Breast cancer ever users		
3,418,124	79.3%	2,710,572		
Adjusted estimate of cases if no use of COCs →		2,277,792	1.19	RR
Excess cases →		432,780		
Annual cost per patient of breast cancer →		$22,127		
Estimated total costs →		$9,576,133,158		

Cervical Cancer

A recent study in Canada (Pendrith 2016) on the costs of invasive cervical cancer treatment noted: "The mean overall medical care cost was $39,187 [standard error (se): $1,327] in the 1st year after diagnosis. … At 5 years after diagnosis, the mean overall unadjusted cost was $63,131 (se: $3,131), and the cost adjusted for censoring was $68,745 (se: $2,963)." For these calculations we will assume a cost of $39,187 annually for incident cases and $13,749 (=$68,745/5) annually for prevalent cases of invasive cervical cancer. According to the NIH SEER statistics[159], the incidence of invasive cervical cancer is 7.4 per 100,000 person-years. According to the American Cancer Society[160], it is estimated that 13,170 women will be diagnosed with invasive cervical cancer in the USA in 2019. In 2015, there were an estimated 257,524 women living with invasive cervical cancer in the United States. According to the best epidemiology studies noted in Table 6 (Roura 2016) the relative risk of ever use of COCs for the development of invasive cervical cancer is 1.6 and the RR for current use is 2.2. Based on this information, the estimated increase in cost from use of COCs due to incident cases of cervical cancer is ~$33 million (Table 19).

Table 19 – Estimated Economic Impact of COCs due to Increased Incidence of Cervical Cancer

Women of reproductive age	Number on the pill	Incidence		
61,000,000	9,699,000	0.000074		
Estimated women on the pill at risk →		718		
Adjusted estimate of cases →		1,579	2.2	RR
Excess cases →		861		
Annual cost per patient of cervical cancer →		$39,187		
Estimated annual costs →		$33,750,635		

To evaluate the impact of "ever use" of COCs on prevalent cervical cancer, we noted that the best study (Roura 2016) showed a 1.6 relative risk of cervical cancer with COCs. According to the SEER statistics, there are currently 257,524 prevalent cases of cervical cancer in the USA. The estimated increase in cost from treatment of the excess cases of cervical cancer is estimated to be ~$1 billion annually (

Table 20).

[159] https://seer.cancer.gov/statfacts/html/cervix.html.
[160] https://www.cancer.org/cancer/cervical-cancer/about/key-statistics.html.

Table 20 – Estimated Economic Impact of COCs due to Increased Prevalence of Cervical Cancer

Prevalent cases of breast cancer	Ever use of COCs	Cervical cancer ever users		
3,418,124	79.3%	257,524		
Adjusted estimate of cases if no use of COCs →		204,217	1.6	RR
Excess cases →		76,581		
Annual cost per patient of cervical cancer →		$13,749		
Estimated total costs →		$1,052,914,912		

Crohn's Disease

A recent study in the US (Rao 2018) estimated the 5-year cost of the treatment of Crohn's disease as $116,838 per patient (interquartile range of $45,643–$240,398; annual cost $23,368). This was higher with worsening disease activity. According to the Centers for Disease Control (CDC), the incidence of Crohn's disease is 3.1 to 14.6 cases per 100,000 person-years[161]. According to the best epidemiology studies noted in Table 7 (Khalili 2013; García Rodríguez 2005), and the best meta-analysis (Cornish 2008), the relative risk of current COC use is 1.46–2.82 for the development of Crohn's disease. Based on this information, the estimated increase in cost just from treatment of the excess cases of Crohn's disease, only looking at current use and not past use of COCs, is between $3 million and $60 million annually (Table 21).

Table 21 – Estimated Economic Impact of COCs due to Increased Incidence of Crohn's Disease

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000031	0.000146		
Estimated women on the pill at risk →		301	1,416		
Adjusted estimate →		439	2,067	1.46	Low RR
Adjusted estimate →		848	3,993	2.82	High RR
Excess cases →		138	651	Low RR	
Excess cases →		547	2,577	High RR	
Annual cost per patient of Crohn's disease →		$23,368			
Estimated annual costs →		$3,231,920	$15,221,300	Low RR	
Estimated annual costs →		$12,787,162	$60,223,406	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort study (Khalili 2013) and meta-analysis (Cornish 2008) showed a 1.43 and 1.44 relative risk of Crohn's disease. According to the Centers for Disease Control (CDC), the prevalence of Crohn's disease in adults is 201 cases per 100,000 person-years[162]. Taking the lower number of 1.43, the estimated increase in cost from treatment of the excess cases of Crohn's disease due to COC use is approximately $1.9 billion annually (Table 22).

Table 22 – Estimated Economic Impact of COCs due to Increased Prevalence of Crohn's Disease

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	0.000201		
Estimated women on the pill at risk →		190,144		
Adjusted estimate →		271,906	1.44	RR
Excess cases →		81,762	1.44	RR
Annual cost per patient of Crohn's disease →		$23,368		
Estimated total costs →		$1,910,583,605	1.44	RR

Ulcerative Colitis

A recent study in the US (Cohen 2015) noted that compared with controls, patients with UC had higher adjusted total direct ($15,548 vs $4812) and indirect costs ($4125 vs $1961) annually. This implies a total annual increase in cost of ~$12,900 for UC. This was higher with worsening disease activity. According to the Centers for Disease Control (CDC), the incidence of UC is 2.2 to 14.3 cases per 100,000 person-years[163]. According to the best epidemiology studies noted in Table 8 (Khalili 2013; García Rodríguez 2005), and the best meta-analysis (Cornish 2008) the relative risk of current COC use 1.22–1.58 for the development of UC. Based on this information, the estimated increase in cost just from treatment of the excess cases of UC, only looking at current use and not past use of COCs is between $605,000 and $10 million per year (Table 23).

[161] https://www.cdc.gov/ibd/IBD-epidemiology.htm.
[162] https://www.cdc.gov/ibd/IBD-epidemiology.htm.
[163] https://www.cdc.gov/ibd/IBD-epidemiology.htm.

Table 23 – Estimated Economic Impact of COCs due to Increased Incidence of Ulcerative Colitis

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000022	0.000143		
Estimated women on the pill at risk →		213	1,387		
Adjusted estimate →		260	1,692	1.22	Low RR
Adjusted estimate →		337	2,191	1.58	High RR
Excess cases →		47	305	Low RR	
Excess cases →		124	804	High RR	
Annual cost per patient of ulcerative colitis →		$12,900			
Estimated annual costs →		$605,567	$3,936,184	Low RR	
Estimated annual costs →		$1,596,494	$10,377,212	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort study (Khalili 2013) showed a 1.18 relative risk of UC. The estimated increase in cost of the excess cases of UC due to use of COCs is approximately $522 million annually (Table 24).

Table 24 – Estimated Economic Impact of COCs due to Increased Prevalence of Ulcerative Colitis

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	0.000238		
Estimated women on the pill at risk →		225,146		
Adjusted estimate →		265,672	1.18	RR
Excess cases →		40,526	1.18	RR
Annual cost per patient of ulcerative colitis →		$12,900		
Estimated total costs →		$522,789,187	1.18	RR

Systemic Lupus Erythematosus

A recent study in the US (Chen 2015) noted that mean total health care costs were $21,535 among all SLE patients over the 1-year study period. According to the Centers for Disease Control (CDC), the incidence of SLE is 6.5–10.6 cases per 100,000 women-years[164]. In terms of prevalence, "A conservative estimate suggests a prevalence of 161,000 with definite SLE and 322,000 with definite or probable SLE." According to the best epidemiology studies noted in Table 9 that evaluated current use of COCs (Bernier 2009), the relative risk of current COC use is 1.45 – 2.52 for the development of SLE. Based on this information, the estimated increase in cost just from treatment of the excess cases of SLE, only looking at current use and not past use of COCs, is $6.1 million to $33.6 million annually (Table 25).

Table 25 – Estimated Economic Impact of COCs due to Increased Incidence of Systemic Lupus Erythematosus.

Women of reproductive age	Number on the pill	Low incidence	High incidence		
61,000,000	9,699,000	0.000065	0.0001065		
Estimated women on the pill at risk →		630	1,028		
Adjusted estimate →		914	1,491	1.45	Low RR
Adjusted estimate →		1,589	2,591	2.52	High RR
Excess cases →		284	463	Low RR	
Excess cases →		958	1,563	High RR	
Annual cost per patient of SLE →		$21,535			
Estimated annual costs →		$6,109,388	$9,963,002	Low RR	
Estimated annual costs →		$20,636,155	$33,652,807	High RR	

To evaluate the impact of "ever use" of COCs, we noted that the best cohort studies (Costenbader 2007; Bernier 2009) showed a relative risk of SLE 1.19–2.3. The estimated increase in cost of the excess cases of SLE due to use of COCs is approximately $439 million–$1.55 billion annually (Table 26).

[164] https://www.cdc.gov/lupus/facts/detailed.html.

Table 26 – Estimated Economic Impact of COCs due to Increased Prevalence of Systemic Lupus Erythematosus.

Women ≥ 18 in 2010 Census	Ever use of COCs	Prevalence		
119,292,801	94,599,191	161,000		
	Estimated women on the pill at risk →	127,673		
	Adjusted estimate →	107,288	1.19	Low RR
	Adjusted estimate →	55,510	2.3	High RR
	Excess cases →	20,385	1.19	Low RR
	Excess cases →	72,163	2.3	High RR
	Annual cost per patient of SLE →	$21,535		
	Estimated total costs →	$438,985,908	1.19	Low RR
	Estimated total costs →	$1,554,030,205	2.3	High RR

Depression

The most reliable study (Skovlund 2016) indicated a 1.1 RR for depression with COCs and a 1.2 RR with POCs. This study evaluated women aged 15-34 and then followed them for a mean of 5 years. According to the information from Brody (Brody 2018), the prevalence of depression in women aged 20-39 is 10.1%. An analysis of medical claims conducted by insurer Blue Cross Blue Shield (Blue Cross Blue Shield 2018) found that "in 2016, Blue Cross plans spent $10,673 on those diagnosed with 'major depression' compared to $4,283 on those without a depression diagnosis." With this information, and noting from the census data (Howden 2011) that there are ~52 million women aged 15-39, we calculate that the excess annual cost of depression attributable to COCs is ~$2.4 billion (

Table 27) and from POCs is ~$937 million (Table 28).

Table 27 – Estimated Economic Impact of COCs due to Increased Prevalence of Depression

Women aged 15-39	51,877,977
Percent with depression	10.1%
Women aged 15-39 with depression	5,239,675.68
Ever use of COCs	79.30%
15-39 y.o. COC users with depression	4,155,063
RR of depression with COC use	1.1
Adjusted estimate →	3,777,330
Excess cases →	377,733
Estimated individual annual costs →	$6,390
Estimated total annual costs →	$2,413,713,761

Table 28 – Estimated Economic Impact of POCs due to Increased Prevalence of Depression

Women aged 15-39	51,877,977
Percent with depression	10.1%
Women aged 15-39 with depression	5,239,675.68
Ever use of POCs	16.80%
15-39 y.o. COC users with depression	880,266
RR of depression with POC use	1.2
Adjusted estimate →	733,555
Excess cases →	146,711
Estimated individual annual costs →	$6,390
Estimated total annual costs →	$937,482,772

Multiple Sclerosis

As the most rigorous cohort studies did not show an increase in the risk of developing multiple sclerosis a rigorous cost analysis was not performed. However, using the information from the best case-control study (Hellwig 2016), an increased odds ratio of 1.51 was noted. If this is assumed to be accurate, this can be used along with a study of total MS costs from 1997-2013 (Chen 2017). They noted that, "The total charges on managing MS range from $161 million in 1997 to $755 million in 2013." Conservatively assuming steady costs since 2013, we can calculate that 79.3% of those costs were incurred by women who were "ever users" of COCs. This yields $598,715,000. If these women had not used COCs there would have been a proportionate reduction in costs of $202,215,000 ($598,715,000–($598,715,000/1.51)).

Interstitial Cystitis

According to one recent paper (Tung 2017) on average, having interstitial cystitis was associated with $7,223 higher total health care costs annually than not having IC. The prevalence of interstitial cystitis has been estimated at 2.7% using a high specificity definition (McLennan 2014) while another study in a managed care population (Clemens 2005) indicated (depending on the definition) a prevalence between 45 and 197 per 100,000 women. Using the most conservative estimate (Champaneria 2015) "ever use" of COCs is associated with an OR of 2.31 for interstitial cystitis. Assuming 61 million women of reproductive age, with a 79.3% of exposure to COCs, this suggests ~11,500 excess cases (using a prevalence of interstitial cystitis of 45/100,000) to ~50,500 (using a prevalence of interstitial cystitis of 197/100,000). This yields an annual cost of $83–$365 million (Table 29).

Table 29 – Estimated Annual Economic Impact of COCs due to Increased Prevalence of Interstitial Cystitis

Low prevalence of interstitial cystitis	0.00045
High prevalence of interstitial cystitis	0.00197
Women of reproductive age	61,000,000
Number with ever use of the pill	48,373,000
# of Women with interstitial cystitis low prevalence	21,768
# of Women with interstitial cystitis high prevalence	95,295
OR	2.13
Excess cases of interstitial cystitis low prevalence	11,548
Excess cases of interstitial cystitis high prevalence	50,555
Annual cost	$7,223
Annual cost of interstitial cystitis low prevalence	$83,412,664
Annual cost of interstitial cystitis high prevalence	$365,162,106

Osteoporotic Bone Fracture Risk

According to a recent review (Ballane 2017), in North America the incidence of osteoporotic vertebral fractures is 837 to 1,083 cases per 100,000 women per year (mean of 960 per 100,000 per year) as standardized to 2015. The annual excess cost of care for women with osteoporotic vertebral fractures was estimated to be $11,655 per year (Kilgore 2009). Using the most relevant relative risk of 1.07 (Barad 2005), this implies an annual cost of ~$308 million dollars in the US from COC use (Table 30).

Table 30 – Estimated Economic Impact of COCs due to Increased Annual Incidence of Vertebral Fractures

Women ≥ 50 in 2010 Census	Ever use of COCs	Incidence of osteoporotic vertebral fractures		
53,151,456	42,149,105	0.0096		
Estimated women on the pill with Fx →		404,631		
Adjusted estimate →		378,160	1.07	RR
Excess cases →		26,471		
Annual cost per patient of osteoporotic vertebral fractures →		$11,655		
Estimated total annual costs →		$308,521,992		

The best cohort study on fracture risk with progesterone-only contraceptives (POCs) showed a RR of 1.51 for ever use of DMPA (Lanza 2013), the most widely used POC. Assuming 16.8% of women have used POCs this yields an annual cost of ~$290 million dollars in the US from POC use (

Table 31).

Table 31 – Estimated Economic Impact of POCs due to Increased Annual Incidence of Vertebral Fractures

Women ≥ 50 in 2010 Census	Ever use of POCs	Incidence of osteoporotic vertebral fractures		
53,151,456	8,929,445	0.0096		
Estimated women on the pill with Fx →		85,723		
Adjusted estimate →		60,796	1.41	RR
Excess cases →		24,926		
Annual cost per patient of osteoporotic vertebral fractures →		$11,655		
Estimated total annual costs →		$290,517,770		

Body Mass

The costs of the effects on body mass were not calculated, but these effects are contributory to atherosclerosis and cardiovascular events, which are discussed below.

Urogenital Effects

The medical and societal costs of the urogenital effects of hormonal contraceptives were not calculated as, although there are measurable costs, they are not felt to be significant.

Venous Thromboembolism, Atherosclerosis and Cardiovascular Disease

About 1 in every 4 female deaths is due to heart disease; it is the leading cause of death for women in the U.S.[165] A review of recent population studies revealed that the overall prevalence of Peripheral Arterial Disease (PAD) for women is 15.6% (compared to 13.4% for men).[166] In 2008, coronary heart disease was prevalent in 7.5 million women.[167] The total mean direct medical costs for cardiovascular disease (CVD) is $18,953 annually (Nichols 2010). Using the median relative risk of the most popular birth control brands, the RR is 1.8 (Table 32).

Table 32 – Estimated Economic Impact of COCs due to Increased Incidence of Cardiovascular Disease

Coronary heart disease	Ever use of COCs	CHD in ever users		
7,500,000	79.3%	5,947,500		
Adjusted estimate of cases if no use of COCs →		3,304,167	1.8	RR
Excess cases →		2,643,333		
Annual cost per patient for CVD →		$18,953		
Estimated total costs →		$50,099,090,349		

A more conservative estimate would assume that the increased risk for cardiovascular disease is limited to women aged 15–49 years, which was the group studied by Lidegaard (Lidegaard 2012). According to the US Census in 2010, population is broken down by age group (Howden 2011). The rate of cardiovascular events is similarly broken down by Lidegaard (Lidegaard 2012). Thus, the number of cases by age group is shown in Table 33.

Table 33 – Cardiovascular Events in Women by Age Group

Census data		Events per 100,000 person-years (Lidegaard 2012)		Events per year	
Age group	Number of women	Myocardial infarction	Stroke	Myocardial infarction #	Stroke #
15 to 19 years	10,736,677	0.4	3.4	43	365
20 to 24 years	10,571,823	0.7	5.6	74	592
25 to 29 years	10,466,258	2.2	10.5	230	1,099
30 to 34 years	9,965,599	5	15.4	498	1,535
35 to 39 years	10,137,620	12.2	23.3	1,237	2,362
40 to 44 years	10,496,987	25.4	39.2	2,666	4,115
45 to 49 years	11,499,506	38.2	64.4	4,393	7,406
Total number of events per year				9,141	17,473

Using these estimates, with the annual cost of care for cardiovascular disease and the relative risk noted above, this calculates to ~$61 million in excess costs for myocardial infarctions and ~$117 million in excess costs for strokes (Table 34).

[165] https://www.cdc.gov/dhdsp/data_statistics/fact_sheets/fs_women_heart.htm.
[166] https://www.medscape.org/viewarticle/711179_2.
[167] https://www.healthline.com/health/heart-disease/women-statistics-facts#1.

Table 34 – Cost of Cardiovascular Events in Women Attributable to COC use.

	Myocardial infarction	Stroke		
Total events per year	9,141	17,473		
Ever use of the pill	79.30%			
# with events on COCs	7,249	13,856	1.8	RR Ever Use
Adjusted estimate →	4,027	7,697.96		
Excess cases →	3,222	6,158		
Estimated annual costs →	$18,953	$18,953		
Estimated Excess annual costs →	$61,062,935	$116,719,504		

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Certification

We certify that this petition contains all relevant information, including any that may be unfavorable to the petition, that we were able to obtain.

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The Impact of the Pill on Implantation Factors—New Research Findings

For health consumers and health care professionals of an orthodox Judeo-Christian or Islamic tradition, as well as those authentically concerned with the universal respect of unqualified human rights, the asserted capacity of the pill to act as an abortifacient, both in its once-a-day and 'morning-after' permutations, is one of significant moral weight.

The research on 'break-through' ovulation[1,2] leads moralists, philosophers and human rights' advocates to question the use of the title 'contraceptive' to describe the pill. There is tension in this nomenclature. The term 'contraceptive' refers to a drug, device or chemical that prevents the joining of the sperm with the female secondary oocyte (commonly referred to as the ovum).[3]

The problem arises because the female sex cell, the secondary oocyte, may be present in the reproductive tract at or near the time of coitus, hence there exists the possibility that fertilization may occur. Yet, as we will see, the pill alters the receptive structure of the endometrium, making implantation problematical.

But are concerned groups justified in moving from a position which states that the pill sometimes fails to prevent 'ovum' fertilization, with the result that new human life may begin, to the position of claiming that the pill has an abortifacient capacity? The first position notes that ovulation occurs in women on the pill and fertilization may occur, but claims there is no evidence that implantation is impeded. The alternate view considers that because ovulation has been detected and the lining of the womb is in an undeveloped state, human life is imperiled.

This is a seismic shift in outlook. What merit is there in this latter claim other than supposition or suspicion? Is the pill tarnished with the title of abortifacient on conjecture rather than on fact?

This paper will seek to clarify these issues. I will concentrate in some depth on a variety of the implantation factors associated with the microenvironment of the endometrial epithelium. Discussion will also be focused on the mechanism(s) of hormonal dialogue between the 5-7 day old human embryo (the blastocyst) and the cells which line the endometrium. I will also cover the impact of above normal (supraphysiological) levels of estrogen and progesterone on these implantation factors and the role of the pill hormones on the integrity of the endometrium. Particular attention will be given to the impact of the pill on cyclical development of endometrial thickness, and the relationship of this uterine feature to the success of implantation of the human embryo. Central to these issues will be a review of the research on 'break-through' ovulation (also known as 'escape-ovulation'), an event which must occur, otherwise all concerns concerning the pill as an abuser of human rights would be shown to be empty.

This paper is of necessity detailed. I hope that the employment of suitable analogies, as well as bracketed discussion of medical terms or concepts, will make it accessible to the scholar and lay reader alike.

1.1 EXECUTIVE SUMMARY

The process of implantation of the human embryo into the lining of the womb is a very complex and delicate one.[4] Proper attachment and successful implantation is under the guidance and control of a vast array of 'implantation factors' such as interleukin-1 β (IL-1β)[5] platelet-activating factor (PAF),[6,7] insulin-like growth factor (IGF),[8] leukemia inhibition factor (LIF),[9] tumor necrosis factor α (TNF α).[10]

Many of these chemical factors participate in a process referred to in the medical journals as 'cell-signalling', a process which involves the new human embryo and the cells of the lining of the womb chemically communicating with each other.[11, 12,13,14] The purpose of this chemical communication is to create an optimally advantageous endometrial environment at the time the human embryo attempts to implant.

Aside from this bio-chemical embryo/uterine-cell communication, successful implantation of the human embryo is dependent also upon a class of molecules known as integrins. Integrins are cell-adhesion molecules found in a 'mirror' fashion on both the human embryo and the lining of the womb.[15,16] These integrins bind onto each other, via gluco-proteins (e.g. fibronectin). The success or otherwise of this binding process is intimately linked to the ongoing success or otherwise of the pregnancy.

The reader will note that I am using the orthodox understanding of the term 'pregnancy'. This definition dates the beginning of the pregnancy from the moment of fertilization. I do not use, nor do I accept the minority view,

influenced as it is by the politics of abortion, that dates a pregnancy from the time of implantation.

1.2 THE RE-DEFINING OF PREGNANCY TERMINOLOGY

Notwithstanding the embryonic, linguistic and time-honoured orthodoxy of 'pregnancy', increasingly frequent attempts have been made to redefine all aspects of pregnancy, but most particularly, when pregnancy begins. The reason for this move is clear; by redefining pregnancy—when it begins, the nature of the embryo etc—the way will be made smooth for the more rapid introduction of RU-486, the morning-after pill, anti-HCG vaccines, anti-implantation factor drugs and other embryocidal drugs. Unwittingly or otherwise, the end result is a semantically based desensitization of the moral conscience of the community.

The following is an indicative selection of quotes to illustrate my point.

> The prevention of pregnancy before implantation is contraception and not abortion.[17] (Glasier, *NEJM,* 1997)

> Predictably, some opponents of abortion allege that emergency contraception is tantamount to abortion . . . even if emergency contraception worked solely by prevention the implantation of a zygote, it would still not be abortifacient... Pregnancy begins with implantation, not fertilization . . . fertilization is a necessary but insufficient step toward pregnancy.[18] (Grimes, *NEJM,* 1997)

> Emergency contraception works by inhibiting or delaying ovulation or by preventing implantation. Despite some assertions to the contrary, it is not itself a form of abortion.[19] (Guillebaud, *Lancet* 1998)

These opinions are starkly at odds with embryology[20] and etymology.[21]

Before examining these features in more detail, and the relational involvement of the pill, it may be of some benefit to propose an analogy to assist in the understanding of the various implantation factors and the role of integrins.

Consider the example of a space shuttle, low on fuel and oxygen, urgently needing to dock with the space station. The mother ship and the shuttle communicate with each other so that the shuttle knows which docking bay to go to. Importantly, the mother ship knows which bay to make ready. Successful communication is imperative. If this electronic communication fails (disrupted embryo-uterine 'cell-talk') the shuttle may go to the wrong docking bay, fail to attach to the mother ship, drift away, with the result that the crew dies from a lack of food and oxygen. Alternatively, the shuttle might go to the right bay but find that all the docking apparatus is not in place. Again, the attachment between the two fails due to faulty communication and the crew dies. This role of embryo/endometrium communication is fulfilled by implantation factors such as interleukin, TNF, NDF and PAF. To continue the analogy, integrins could be thought of as grappling hooks that 'hold' the human embryo onto the womb whilst the process of implantation is completed.

This then is a brief overview of this review paper. I would like now to analyse these issues in more depth, looking at the specific role and activity of the main implantation factors covered in the research literature. As well, I will expand on the interaction between these factors and the steroidal hormones: estrogen, and its artificial copies (principally ethinylestradiol, ingested via the pill) and progesterone, plus its artificial copies (norethisterone, levonorgestrel, gestodene and desogestrel).

1.3 THE INTERLEUKIN SYSTEM

The interleukin (IL) system, composed of IL-lα, IL-1β and IL-Ira, is both hormonally regulated and of endometrial origin (Simon, 1996).[22] Under *normal* physiological conditions, progesterone increases the production of IL-lα, and IL-lβ from the endometrium[23] and levels of the IL system reach their maximum during the luteal (post-ovulatory) phase of the menstrual cycle.[4]

Of the various components of the interleukin system, research suggests that IL-lβ plays a key role in the proper orientation of the embryo to the uterine lining, a process known as apposition. Recalling our earlier analogy, apposition could be likened to pre-docking maneuvers responsible for correctly aligning the docking ports of mother ship and shuttle.

Within this framework, the role of IL-lβ is thought to be that of a 'signal system' between endometrium and embryo.[25]'... [S]uccess of embryonic implantation relies on a perfect dialogue between good quality embryos and a receptive endometrium'.[26]

Huang and co-workers (1997) have also reported that the IL system is 'an important factor in embryo-maternal molecular communication during the implantation process'.[27]

Whilst normal levels of the ovarian hormones estrogen and progesterone have a beneficial effect on the levels of IL-1β, excessive hormonal levels, known as supra-physiological steroid levels, have been shown to cause a reduction in the levels of IL-lβ. As a result, the rate of implantation drops significantly. Simon and co-workers *(J Reprod Immun,* 1996) have shown that there is an inverse relationship between estrogen and progesterone levels, and the levels of IL-lβ (as estradiol levels increase, implantation success decreases).[28]

The direct consequence of these findings, as they relate to the maintenance of pregnancy, are set out by Carlos Simon:

> ... we have shown prospectively that suprahysiological serum E2 (estradiol) levels during the pre-implantation period are responsible for the impairment of embryonic implantation in patients undergoing I.V.F. It is possible that above normal (supraphysiological) serum E2 levels impair implantation through disrupting regulation of uterine paracrine factors; specifically, the IL-1 system is one possible candidate when considering what is reported in the present study.[29]

The term 'paracrine' refers to the effect(s) that are caused by hormones but are localized to cells only in the immediate vacinity,[30] i.e., the endometrium, rather than the more normal, wider area of bodily influence that characterizes hormones.[31]

Simon's research indicated that excessive estradiol (an estrogen) levels interfere with implantation as a consequence of disruption to the IL-1 system. I.V.F. research has shown that high levels of estradiol (E2) result in a poor implantation rate of 8.5% whereas reduced E2 levels increased the successful rate of implantation to 29.3%.[32]

As Simon and co-workers noted, 'High E2 levels, which are known to be interceptive, and altered E2/progesterone ratios, which also are associated with the impairment of endometrial receptivity, are the main factors affecting endometrial receptivity in high responders.'[33]

The use of the word 'interceptive' is significant. Professor Rahwan, professor of Pharmacology and Toxicology, Ohio State University, defines interception as the 'interference with the implantation (nidation) of an already fertilized ovum, and, from a biological standpoint, must therefore be an early abortifacient approach'.[34]

This research by Simon finds its importance within the context of the emerging use of the pill in high doses as a post-coital or 'morning-after' pill (MAP). The MAP regime comprises the ingestion, within a time-frame of 12 hours, of approximately 10 times more estrogen and 10-20 times more progesterone than a woman would take via the normal once-a-day pill (depending on the brand used). These increased levels are obviously supra (above) physiological levels.

As previously outlined by Simon, the disruptive effect on implantation rates caused by high levels of estradiol, or incorrect estradiol/progesterone ratios, means it is biologically plausible to suggest the 'morning-after pill' (MAP) is an abortifacient-empowered medication because of its capacity to interfere with the interleukin system.

Further supporting this assertion is research by Swahn *et al.* (1996), which showed the administration of the MAP caused a suppression of the LH surge, decreased the pregnandiol levels and increased the estrone levels (Fig 1, p. 741).[35] These alterations to the normal menstrual cycle hormonal patterns had an impact on the development of the endometrium.

> An endometrial biopsy was taken one week after treatment. Although it was difficult to date the biopsy in some women because of the absence of a discernible LH peak, the conclusion was that the endometrium showed significant alterations in endometrial development with a dissociation in maturation of glandular and stromal components [36]
>
> .

The authors then, in a seemingly contradictory manner, suggest that the 'relatively minor changes in endometrial development does not seem sufficiently effective to prevent pregnancy'.[37] This statement would appear to undermine any claim that the MAP acts in part via an abortifacient mechanism. Further reading reveals that the researchers did not investigate the 'biochemical effects (of the pill) on molecular levels on the endometrium'.[38] That is, the researchers did not investigate the hormonal impact of the MAP on the various implantation factors.

In my view, this omission negates their attempts to minimize the abortifacient significance of the 'relatively minor changes in endometrial development' caused by the MAP. As will be seen later, relying only on measures of endometrial thickness cannot accurately assess the precise conditions needed for successful implantation—this exclusive approach fails to take heed of the implantation factors which are the second, vital characteristic associated with successful implantation.

1.4 PLATELET-ACTIVATING FACTOR (PAF)

Another implantation factor which is associated with successful uterine receptivity of the human embryo is platelet-activating factor (PAF).[39] PAF interacts with PAF receptors located on the endometrium. To recall, receptors are bio-chemical binding sites, located on the surface of cells, which are specifically designed to interact exclusively with a specific chemical, in this case PAF. When PAF attaches to the receptor, a message is conveyed to those cells.[40]

The effect of PAF upon the endometrium is to cause a release of nitrous oxide (NO), leading to vascular dilation and increased vascular permeability of the blood vessels of the endometrium[41] The fact that chemical blockage of the PAF binding site (receptor) on the endometrium inhibits implantation supports the view that the PAF receptor has a critical role in uterine receptivity[42]

PAF is also involved in the cyclical development of the endometrium.[43,44] Not surprisingly, the levels of the receptors for PAF vary throughout the menstrual cycle, with the highest endometrial levels detected during the mid-late proliferative phase (i.e., the days preceding ovulation) and the late secretary phase,[45] when the endometrium is approaching or at its state of maximum monthly development. These findings are consistent with PAF having a preparatory role for uterine reception of the human embryo.

As was the case with the interleukin system, control of PAF is under the control of ovarian hormones, estradiol and progesterone.[46] As Ahmed has noted: 'PAF production has been shown to be regulated by ovarian hormones .. .'[47]

Given the role of ovarian hormones on the activity of PAF and its receptor within the endometrium, it is biologically plausible to suggest that irregular uterine hormone levels, caused by the pill, may have a negative impact on uterine preparedness for implantation. Supporting this view is the work of Rabe and co-workers, who reported a decrease in endometrial thickness in women taking the pill, during the days when implantation would occur.[8]

Specifically, these researchers showed that there was, for some pill users, a 50% reduction in endometrial development when compared to that seen in the control (non-pill using) group.[49] Therefore, it is reasonable to conclude there is an adverse impact upon the express of PAF receptors. Indeed, given the hormonal influence exerted by estrogen, it would be biologically illogical to conclude no damage to the expression of endometrial PAF receptors.

1.5 THE EFFECT OF MISSED FILLS ON OVULATION

For the pill to exhibit the characteristic of an abortifacient, one biological event is essential: ovulation. The crucial

question is this—does break-through (or escape) ovulation occur during regular pill ingestion?

Grimes *et al. (Obstet Gynecol,* 1994) had previously reported that 'suppression of follicular development is incomplete with contemporary low-dose pill'.[50]

Grimes' study was characterized by a high rate of patient compliance, meaning that the women involved in the study adhered to the research protocol of daily ingestion of the pill.[51] Yet, escape-ovulation was detected even within the context of a rigorously scrutinized scientific study.

These facts argue strongly in favour of escape-ovulation also occurring within the general populace of women on the pill. This latter group of women are not necessarily as highly motivated as those participating in a scientific study. To adhere to a tedious daily, monthly, yearly regime of pill ingestion, without supervision is, in the words of one feminist writer a 'bore and a chore'.[52] Because daily pill ingestion is so onerous, patient compliance will be less than the necessary ideal. However, does the occasional failure to take the pill mean that 'escape ovulation' will increase in some proportional fashion?

In an attempt to determine the frequency of escape-ovulation under more realistic conditions, researchers have constructed experiments that required women in the study to deliberately miss one or more days of the pill. A variety of tests, including ultrasound of the ovaries, estradiol (E2), progesterone (P) levels and LH (leutinizing hormone) measurements were used to determine if ovulation had occurred.

Hedon and co-workers (1992) tested 47 young, healthy women who missed between 1 and 4 days tablets starting from day 1 of a new cycle. 'None of the patients experienced normal ovulation' though one, who missed 3 tablets at the beginning of the cycle, 'had a follicular rupture', but no LH surge or progesterone increases, factors usually associated with normal ovulation[53] Note that this study was for only one cycle. Limiting the study to one cycle was a study weakness, because any follicles which may have ruptured during the normal 7 pill free days between cycles would not be detected.

Earlier, Hamilton (1989) had performed a similar study but extended the observations for two consecutive months. Of 30 women in the study, one had a probable ovulation, due to one deliberately omitted tablet on day one of the *second* cycle.[54]

More recently, Letterie (1998) published the results of a study employing a new, reduced dosage formulation of the pill. Ten women, divided into 2 groups, used two slightly different formulations comprising a delayed start, limited midcycle use of estrogen and progesterone. Each of the two treatment groups was monitored for 2 consecutive cycles. In total, 30% of cycles exhibited ovulation, all of which occurred in the *second* cycle.[55]

It is revealing to look more closely at the data for the two groups. In group one, ovulation occurred in 10% of cycles (1 in 10 cycles). This group took 50mcg ethinyl estradiol/lmg norethinodrone for days 6-10 and 0.7mg norethinodrone for days 11-19. Group two took 50mcg ethinyl estradiol/lmg norethinodrone for days 8-12, and 0.7mg norethinodrone only for days 13-21, 'five ovulation(s) occurred in 10 cycles'.[56] This is an ovulation rate of 50%. This study did not investigate implantation; all participants used barrier contraceptives, or abstinence (Private correspondence).[57]

It should be noted that these research findings, conducted under ideal research conditions, represent the best possible outcome in terms of ovulation suppression by the pill. Yet these results do not faithfully replicate real-life because they do not take into account such common events as gastro-intestinal illness or drug interactions. Stomach upset decreases drug absorption, thus loosening the hold over ovulation otherwise exerted by the pill hormones. Likewise, drug interactions decrease the amount of active pill hormone available to act in a suppressant manner upon the ovaries.[58,59] Other researchers and I are of the view that these two issues would contribute to an increase in the frequency of escape-ovulation.[60]

1.6 PILL CONTROL OVER OVARIAN FOLLICULAR DEVELOPMENT

Based upon my 20 years experience as a community pharmacist, I believe the commonly held view is that the pill fully stops ovulation (anovulation). Yet this view is wrong. The recent work by Rabe *et al.* (1997) contradicts this common misunderstanding. Following are some salient points from this research.

- Pre-ovulatory follicular cysts (> 20mm) occurred in 7.3% of 329 pill users enrolled in the study.[61] This size of follicle is identified with an increased rate of escape-ovulation.[62]
- For non-pill users, the rate of follicular cysts was 13.9%.
- Some women, notably those on triphasic formulations, had follicles measuring 60mm.
- Estradiol was present at higher levels (in pill users with enlarged follicles) than in non-pill users (who also had enlarged follicles). The respective levels were 153 pg/ml and 126 pg/ml.[63]

The estradiol level of 153 pg/ml, seen in pill users with enlarged follicles, is important, as it is close to the 'threshold level 150 to 200pg/ml', which, if persisting for approximately 36 hours, triggers ovulation.[64]

As a summary of their research, Rabe noted: 'Analysis of the ovarian activity in the current study demonstrated that the total number of developing follicles increased rather than diminished during OC use, without marked differences between OCs'.[65]

This research underscores the pill's precarious hold over ovulation suppression. It is an event endeavouring to occur. The intervention of a variety of 'lifestyle' factors such as missed doses, drug interactions or gastro-intestinal upset, can act to loose the hold exerted by the pill over natural ovarian function.

As a footnote to this discussion, the FDA approved, in late 1998, a low dose estrogen formulation of the pill (norethinodrone acetate, 1 mg; ethinyl estradiol 20 mcg). Similar low-dose estrogen formulations are also now available in Australia.[66] The frequency of escape ovulation can only be expected to increase in this situation of reduction hormonal ingestion.

1.7 ENDOMETRIAL THICKNESS AND IMPLANTATION

Thus, the question arises: will a low dose pill, more inclined than not to permit escape-ovulation, increase the frequency of implantation failure due to a under-developed endometrium? The medical literature indicates that there is a critical thickness of the endometrium needed to sustain implantation of a human embryo.

Issacs *(Fert Steril,* 1996) reported that an endometrial thickness of at least 10mm or more, around the time of ovulation, 'defined 91% of conception cycles'.[67] Spandorfer *(Fertil Steril,* 1996) noted that 97% of abnormal pregnancies, defined as Fallopian tube lodgment or spontaneous abortion, had endometrial thickness of 8mm or less. [68] Shoham *(Fert Steril,* 1991) reported that a mid-luteal thickness of 11 mm or more 'was found to be a good prognostic factor for detecting early pregnancy' but no pregnancies were reported in an ovulation induction programme 'when the endometrial thickness was less than or equal to 7mm'.[69]

The mid-luteal phase of the menstrual cycle, around day 20, is referred to in the medical literature as the window of expected implantation.[70,71]

Gonen *(Journ In Vitro Fert Embryo Transf,* 1990) also reported that 'endometrial thickness was significantly greater in the group of patients who achieved pregnancy than in the group who did not'.[72] Implantation failure was associated with endometrial thickness of approximately 7.5mm, success with endometrial thickness of approximately 8.5-9mm.

These study results, which indicate a normative endometrial thickness of around 8.5mm for successful implantation, are central to any claimed interceptive/abortifacient capacity of the pill. Research findings from Rabe and co-workers (1997) underscore this point.

Rabe reported that study subjects who took the triphasic levonorgestrel/ethinylestradiol formulation had the highest percentage of follicular cysts with a diameter greater than $20mm^{/3}$ but they failed to develop a median endometrial thickness in excess of 6mm.[74] To recall, follicles of this size are 'thought to be associated with increased risk of escape ovulation'.[75]

The importance of these events is clear; follicles of a suitable size can develop in women taking the pill daily, but endometrial thickness has been shown to be underdeveloped. In the event of follicle rupture and release of an 'ovum', implantation of a human embryo would be greatly hampered. Rabe confirms this very point: '. . . the occurrence of pregnancy would be unlikely because accessory contraceptive mechanisms such as cervical hostility and endometrial suppression are usually in effect'.[76]

It must be pointed out that in this quote Rabe has falsely defined pregnancy as beginning at implantation. Pregnancy begins with the fertilization of the female sex cell (ovum) by sperm, the restoration of the full complement of 23 pairs of chromosomes and thereby the creation of a new human person.

Based upon these findings, a number of issues present themselves:

- An endometrial thickness around 8.5mm has been shown to be associated with successful implantation.
- Low dose triphasic formulations of the pill, the most popular in Australia, fail to completely stop follicular development, the precursor stage to the release of a female sex cell.
- Break-through ovulation is an event straining to occur, even with daily pill ingestion.
- If break-through ovulation were to occur, implantation might fail, because of an endometrium that is too thin.

It is important to note that these four observations exist independently of the impact of the pill on the various implantation factors involved in cell-signaling.

1.8 INTEGRINS

As the aforementioned research indicates, the last few years have seen a remarkable unveiling of the process of implantation of the human embryo into the uterine tissue. A large body of evidence now exists which demonstrates that the process of implantation, rather than being an accidental event dependent on chance, is in fact a multi-factorial, cascading bio-molecular,[77] physiological and hormonal event of spectacular intricacy, complexity, refinement and interdependence.[78] Implantation is not, as one might suppose, akin to two pieces of Velcro fortuitously touching and gripping together. Rather, implantation is, in every sense, as complex, and therefore susceptible to interference, as is the clotting mechanisms of the cardiovascular system.

Beside PAF, the interleukin system and other factors mentioned briefly in the introduction, the class of cell adhesion molecules known as integrins also play a critical role in successful implantation of the human embryo into the endometrium.

As the description of the molecule suggests, the role of integrins is to bind cells together. Etzioni has suggested that integrin facilitated cell adhesion is 'a process that is essential for anchorage' of cells to each other *(Lancet,* 1999).[79]

There are a variety of different types of integrins found within the body—one that plays an essential role in implantation is known as $\alpha v\beta 3$. The medical literature now contains many research papers demonstrating the vital role of this integrin in the process of binding the 5-7 day old human embryo to the endometrium (lining of the womb).

Somkuti and co-workers *(Fert Steril,* 1996) for example reported that integrins 'might prove useful as markers of normal endometrial receptivity'[80] because they have been shown to be absent in women with unexplained infertility and endometriosis.[81]

Similarly, Lessey *(Am J Reprod Immunol,* 1996) reported 'aberrant expression of this integrin is associated with infertility in women'.[82] Widra (*Mol Hum Reprod,* 1997) noted 'the absence of endometrial $\alpha v\beta 3$ during the critical period of implantation ... in women with unexplained infertility and endometriosis'.[83] Others had also commented on the absence or diminution of $\alpha v\beta 3$ in women with recurrent pregnancy loss[84] or unexplained infertility.[85]

Assessing the role of the pill, Somkuti (1996) compared endometrial sampling from women on the pill with samples from non-users and reported integrin expression 'to be altered grossly in OC users'.[86]

Complementing this work were the observations of Yoshimura (1997):'… a loss of normal αvβ3 expression is associated with primary infertility and milder forms of the disease. These observations suggest that this integrin plays a significant role in the implantation process'.[87]

Eric Widra and colleagues (1997), at Georgetown University investigated the role of physiological levels of estrogen and progesterone on the endometrial levels of αvβ3. They reported that estrogen caused a down-regulation in the expression of αvβ3,[88] an important finding in the light of the fact that 'expression of the αvβ3 integrin may, in fact, be necessary for normal implantation to occur.[8]

Castelbaum and co-workers *(J Clin Endo Metab,* 1997) reported the endometrial expression (presence) of αvβ3 was 'reduced by E2 treatment and further suppressed by E2 plus P...'[90]

These results indicate a link between the impact of hormones on the expression of integrins, and the role of integrins in implantation. Whilst the inter-relationship between hormones, integrins and implantation is not yet fully understood,[91] sufficient evidence exists to conclude that the inter-relationship is significant from the perspective of implantation. This is because implantation occurs only 'on or about day 20 of an idealized 28-day menstrual cycle' [92] and the αvβ3 integrin 'is expressed on endometrial epithelial cells only at the opening of the implantation window, on postovulatory day 6'.[93]

1.9 INSULIN-LIKE GROWTH FACTOR (IGF)

The IGF system is an important growth factor, playing a key role in the monthly development of the endometrium and in the process of implantation.[94] There are two subsets, IGF-1 and IGF-2. The first is believed to facilitate the mitotic action of estradiol [E2] in the endometrium, whilst IGF-2 'expressed abundantly in mid-late secretory endometrium, may be a mediator of progesterone action'.[95] Aside from this hormonal aspect, the most abundant expression if IGF-11 is in the columns of the invading trophoblast in the anchoring ville.

From this it can be seen that IGF has a promotional effect upon the process of implantation. But IGF is in turn regulated. 'The biological actions of IGFs are modulated by a family of binding proteins (IGFBPs). The demonstration of IGF and IGFBP transcripts [copying facilities] in pre-implantation embryos indicates that the influence of IGFs and IGFBPs in fetal development begins even prior to implantation'.[96]

Thus far, it can be seen that these factors have a key role to play in both the preparation for and process of implantation. As Han *et al.* have noted: 'Presumably, IGF-II and IGFBPs are used for cell to cell communications between fetal trophoblasts and maternal decidual cells at the feto-maternal interface for placental development and/or function'.[97]

Against this background, the role of the hormones in the pill, particularly their influence over implantation, is important. A number of researchers have shown that the pill causes an increase in IGFBP-1 levels and a decrease in plasma concentrations of IGF-1.[98,99] More specifically, during the pill free-week 'IGFBP-1 was significantly lower on the medication-free day than on day 14 of the cycle . . . The short absence of exogenous estrogen and progestin during the medication-free week also affected IGF-1 levels, which were significantly increased'.[100]

The superabundance of IGFBP induced by the pill has, from an implantation perspective, significance. Giudice has reported that: 'IGFBP's bind IGF's with high affinity and, for the most part, inhibit IGF bioavailability to their receptors for action in their target organs'.[101] Thus, the supraphysiological levels of IGFBP, induced by the pill, may be detrimental to the process of implantation via an inhibitor action on the levels of IGF. Giudice highlights this point: 'IGFBP-1 has been shown to inhibit trophoblast invasion into decidualised endometrial stromal cultures, suggesting that this IGFBP-1 is a maternal "restraint" on trophoblast invasion'.[102]

Aside from the indirect anti-implantation effect of excessive levels of IGFBP upon IGF, IGFBP also has a direct, anti-attachment effect upon the human embryo. 'IGFBP-1 specifically binds to first trimester trophoblast and that it binds to the 'α5β1 integrin in trophoblast. Furthermore, it inhibits trophoblast attachment to fibronectin; another RGB ligand found in the placental bed.'[103]

In summary, the pill causes an increase in IGFBP levels, leading to a decrease in IGF levels. This may have a negative impact upon implantation. IGFBP also may have a direct effect at the level of trophoblast/endometrial integrin binding. More research is required to understand fully the roles of IGF and IGFBP. This represents a new, emerging field of research into the multitudinous factors involved in the process of implantation. Whilst the above research indicates that the pill facilitates anti-implantation endometrial environment, confirming evidence is yet to be found. Hence there exists a reasonable suspicion only, a point made by key researchers in the field.[104]

1.10 CONCLUSION

This discussion has had as its focus the multifactorial nature of embryo implantation. On occasion, this discussion has required detailed analysis of the relevant factors influencing the success of this event. Sometimes it is not possible to speak of these events, centred as they are on the maintenance of human life, without a certain measure of complexity and detail. To those readers who have struggled with this material I apologize.

This paper does not presume to be the final word on this complex and evolving branch of medical knowledge. New research appears almost monthly to illuminate further and sometimes confuse this emerging medical discipline. Nevertheless, I hope I have briefed the reader on issues related to the first right of all humans—the right to stay alive. Some may seek to discount the interceptive/ abortifacient capacity of the pill. For three reasons, this would be a scientifically precarious position to adopt.

First, I am of the view that the preceding evidence strongly argues the case in favour of the pill possessing an interceptive/abortifacient capacity. At the very least, the evidence is repetitive and circumstantial. Indeed, how more clear and straightforward could the issue be than the following statement from Eric Widra and colleagues? 'Demonstration of complimentary integrin expression on preimplantation embryos has further buttressed the argument that these molecules are important for the initiation of pregnancy'.[105]

Second, even researchers view as the new arena of 'contraceptive' research the interrelated system of implantation factors. Carlos Simon and colleagues (*Fertil Sterility,* 1998), after discussing the interdependent relationship between the interleukin-1 system, the avb3 integrin adhesion system and implantation, conclude by stating that the interleukin-1 system would be a promising new area of research apropos the development of new 'contraceptives'.[106] Given this sentiment, I am of the view that anti-interleukin chemicals will be the RU-486 of the next decade.

Third, and most tellingly, the abortifacient capacity of the pill is recognized by those who support abortion. Consider the following, taking from the *Guttmacher Report.* 'The best scientific evidence suggests that ECP's [emergency contraceptive pill] most often work by suppressing ovulation. But depending on the timing of intercourse in relation to a woman's hormonal cycle, they—as is the case with all hormonal contraceptive methods—also may prevent pregnancy either by preventing fertilization or by preventing implantation of a fertilized egg in the uterus' (my emphasis).[107]

Need any more be said?

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Effectiveness of Family Planning Methods

Most Effective

Less than 1 pregnancy per 100 women in a year

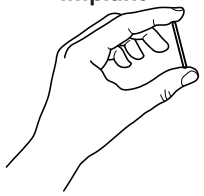
6-12 pregnancies per 100 women in a year

18 or more pregnancies per 100 women in a year

Least Effective

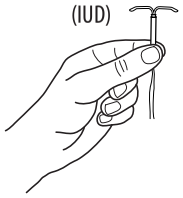
Reversible

Implant



0.05 %*

Intrauterine Device (IUD)



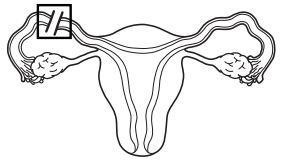
LNG - 0.2 % Copper T - 0.8 %

Permanent

Male Sterilization (Vasectomy)

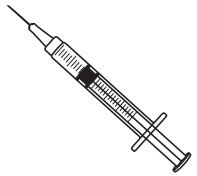
0.15 %

Female Sterilization (Abdominal, Laparoscopic, Hysteroscopic)



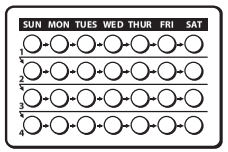
0.5 %

Injectable



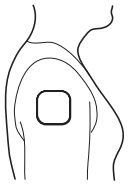
6 %

Pill



9 %

Patch



9 %

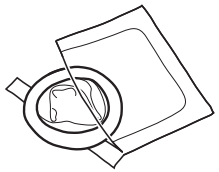
Ring

9 %

Diaphragm

12 %

Male Condom

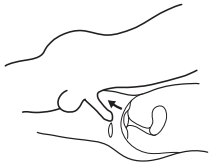


18 %

Female Condom

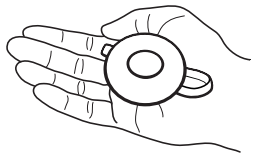
21 %

Withdrawal



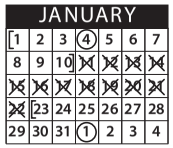
22 %

Sponge



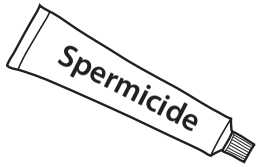
24 % parous women
12 % nulliparous women

Fertility-Awareness Based Methods



24 %

Spermicide



28 %

*The percentages indicate the number out of every 100 women who experienced an unintended pregnancy within the first year of typical use of each contraceptive method.

How to make your method most effective

After procedure, little or nothing to do or remember.

Vasectomy and hysteroscopic sterilization: Use another method for first 3 months.

Injectable: Get repeat injections on time.

Pills: Take a pill each day.

Patch, Ring: Keep in place, change on time.

Diaphragm: Use correctly every time you have sex.

Condoms, sponge, withdrawal, spermicides: Use correctly every time you have sex.

Fertility awareness-based methods: Abstain or use condoms on fertile days. Newest methods (Standard Days Method and TwoDay Method) may be the easiest to use and consequently more effective.

CS 242797

CONDOMS SHOULD ALWAYS BE USED TO REDUCE THE RISK OF SEXUALLY TRANSMITTED INFECTIONS.

Other Methods of Contraception

Lactational Amenorrhea Method: LAM is a highly effective, temporary method of contraception.

Emergency Contraception: Emergency contraceptive pills or a copper IUD after unprotected intercourse substantially reduces risk of pregnancy.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Adapted from World Health Organization (WHO) Department of Reproductive Health and Research, Johns Hopkins Bloomberg School of Public Health/Center for Communication Programs (CCP). Knowledge for health project. Family planning: a global handbook for providers (2011 update). Baltimore, MD; Geneva, Switzerland: CCP and WHO; 2011; and Trussell J. Contraceptive failure in the United States. Contraception 2011;83:397–404.

Part Three

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Links to FDA Petition

FDA Petition to change labeling of hormonal contraceptives:
https://www.regulations.gov/document?D=FDA-2019-P-2289-0001&mc_cid=07303bace3&mc_eid=d7a5cb308e

Links to Petition Correspondence: https://www.regulations.gov/docket?D=FDA-2019-P-2289

Link so you can comment publicly on your experience with hormonal contraceptives:
https://www.regulations.gov/comment?D=FDA-2019-P-2289-0001

Fertility Awareness and Natural Family Planning Methods

These methods have been studied and have failure rates comparable to hormonal contraceptives. The CDC has reported an overall failure rate of 24% because they included in their statistics ALL methods of Fertility Awareness and Natural Family Planning Methods published. These web sites have studied and published their own specific rates. Women learning these methods empower themselves to both postpone and achieve pregnancy.

Billings Ovulation Method:
Teaches women to become aware of their days of fertility through self observation

Billings USA: http://www.boma-usa.org/
Creighton Model FertilityCare System: http://www.creightonmodel.com/
http://www.fertilitycare.org/
Family of the Americas: http://www.familyplanning.net/ (Easiest to use and understand)

Sympto-thermal method: Adds temperature measurement to self observations
Couple to Couple League: http://www.ccli.org/

Sympto-hormonal: Adds measurement of urinary hormones to self observation
Marquette Model: https://www.marquette.edu/nursing/natural-family-planning-model.php