**Republic Of The Philippines
FOOD AND DRUG ADMINISTRATION
Civic Drive, Filinvest Corporate City
Alabang, Muntinlupa City**

PRELIMINARY OPPOSITION TO APPLICATIONS FOR RE-EVALUATION/ RE-CERTIFICATION (With Request for Additional Thirty (30) Days Within Which To File Supplemental and/or Individual Opposition, If Deemed Necessary)

ALLIANCE FOR THE FAMILY PHILIPPINES FOUNDATION, INC., represented by its President and Legal Counsel, Atty. Maria Concepcion S. Noche, respectfully submits the following Opposition to the Applications for Re-Evaluation/Re-Certification of Contraceptive Drugs and Devices ---

1. At the outset, in order to put matters in the proper context, we would like to lay down the important and relevant points in the Supreme Court Decision in the consolidated cases of *Imbong, etc. vs. Hon. Ochoa, Jr., etc. (G.R. No. 204819, 204934, 204957, 204988, 205003, 205043, 205138, 205478, 205491, 205720, 206355, 207111, 207172, 207563)* (the "RH Decision", for brevity). The re-evaluation/re-certification process of the Food and Drug Administration (FDA) is, in fact, a consequence and should be pursuant to the said Supreme Court Decision.

2. The relevant findings and conclusions of the Supreme Court are as follows:

a. LIFE BEGINS AT **FERTILIZATION**, **NOT AT IMPLANTATION.**

- Implantation has been conceptualized only for convenience by those who had population control in mind.

b. THE **FERTILIZED OVUM IS A LIVING HUMAN BEING** WHICH THE STATE HAS THE CONSTITUTIONAL DUTY TO PROTECT EQUALLY WITH THE LIFE OF THE MOTHER.

c. THE PROTECTION OF THE FERTILIZED OVUM MUST BE **FROM FERTILIZATION ALL THE WAY UNTIL IT REACHES AND IMPLANTS IN THE UTERUS.**

d. RH LAW PROHIBITS ABORTION AND MANDATES THAT PROTECTION BE AFFORDED FROM THE MOMENT OF FERTILIZATION.

e. RH LAW ALSO PROHIBITS ABORTIFACIENTS.

f. AS DEFINED UNDER SECTION 4(A) OF THE RH LAW, AN **ABORTIFACIENT** IS ANY DRUG OR DEVICE THAT EITHER:

(a) **INDUCES ABORTION**; OR
(b) **INDUCES THE DESTRUCTION OF A FETUS** INSIDE THE MOTHER'S WOMB; OR
(c) **INDUCES THE PREVENTION** OF THE FERTILIZED OVUM **TO REACH AND BE IMPLANTED** IN THE MOTHER'S WOMB,

UPON DETERMINATION OF THE FDA.

g. THE RH DEFINITION OF ABORTIFACIENT PROTECTS THE FERTILIZED OVUM **FROM FERTILIZATION UNTIL IT REACHES AND IMPLANTS IN THE UTERUS**.

h. CONTRACEPTIVES TO BE INCLUDED IN THE PHILIPPINE NATIONAL DRUG FORMULARY SYSTEM (PNDFS) AND THE ESSENTIAL DRUGS LIST (EDL) ARE THOSE THAT **DO NOT HAVE THE PRIMARY AS WELL AS THE SECONDARY ACTION OF CAUSING ABORTION OR THE DESTRUCTION OF A FETUS IN THE UTERUS OR THE PREVENTION OF THE FERTILIZED OVUM TO REACH AND BE IMPLANTED IN THE UTERUS.**

3. The constitutional **Right to Health** is a component of the **Right to Life**; hence, contraceptives that are made available to the public must be **SAFE** and pose no risks to the people's health.

4. Having declared the RH Law constitutional because of its stated policy to provide only **Non-Abortifacient and Safe** contraceptive drugs and devices, the Supreme Court saw the need to institute various safeguards to ensure such policy is strictly carried out.

5. The **SAFEGUARDS** to ensure that only contraceptive drugs and devices that ARE **NON-ABORTIFACIENT, SAFE AND LEGAL** are procured by government and made available to the public are as follows:

a. FDA MUST TEST AND EVALUATE **ALL CONTRACEPTIVE DRUGS AND DEVICES IN ACCORDANCE WITH THE CONSTITUTIONAL YARDSTICKS AND STANDARDS THAT THE SUPREME COURT HAS LAID DOWN IN THE RH DECISION.** (Protection from Fertilization Until the Uterus).

b. BASED ON ITS EVALUATION AND TESTING, **FDA MUST APPROVE AND CERTIFY** THAT CONTRACEPTIVE DRUGS AND DEVICES ARE **SAFE AND NON-ABORTIFACIENT AND THAT THEY CANNOT BE USED AS ABORTIFACIENTS OR THAT THEY CANNOT ACT AS ABORTIVES (NOT THAT THEY WILL NOT BE USED AS ABORTIFACIENTS**); OTHERWISE, THEY CANNOT BE PROCURED BY THE GOVERNMENT (THRU THE DOH), OR DISTRIBUTED, SOLD OR OTHERWISE MADE AVAILABLE TO THE PUBLIC.

c. THOSE THAT HAVE BEEN DULY APPROVED AND DULY CERTIFIED BY THE FDA MUST BE PROCURED FROM, SOLD, DISTRIBUTED, OR DISPENSED BY, **A DULY LICENSED PHARMACEUTICAL COMPANY AND A DULY LICENSED DRUG STORE, UPON THE PRESCRIPTION OF A QUALIFIED MEDICAL PRACTITIONER.**

d. MOREOVER, THE SUPREME COURT HAS EMPHASIZED THAT **"NOT A SINGLE CONTRACEPTIVE HAS YET BEEN SUBMITTED TO THE FDA PURSUANT TO THE RH LAW".**

6. Therefore, it behooves the FDA to evaluate and test **ALL** contraceptive drugs and devices based on the constitutional yardsticks under the RH Decision, including those that are already being presently sold and made available to the public.

7. Recognizing the gravity of the consequences on the life and health of the public posed by the contracepive drugs and devices, the Supreme Court issued a **WARNING**, thus:

> **"A HEAVY RESPONSIBILITY AND BURDEN ARE ASSUMED BY THE GOVERNMENT IN SUPPLYING CONTRACEPTIVE DRUGS AND DEVICES, FOR IT MAY BE HELD ACCOUNTABLE FOR ANY INJURY, ILLNESS OR LOSS OF LIFE RESULTING FROM OR INCIDENTAL TO THEIR USE."**

1. Sources of Scientific and Technical Information

8. We base our Opposition on available scientific and technical information and evidence. We have judiciously sifted through every possible source which includes the following:

(1) Philippine Food and Drug Administration (FDA) websites (old: as of December 2012, and new: after December 2012).

(2) Various Websites, the five (5) principal of which are:

(i) drugs.com, a website which provides accurate and independent information on more than 24,000

prescription drugs, over-the-counter medicines and natural products which they make available to the general public as well as to health professionals from documents of the U.S. FDA and the drug manufacturers themselves;

(ii) of Medline Plus, which is a public service of the U.S. National Library of Medicine and the National Institutes of Health;

(iii) of dailymed, which is also a public service of the U.S. National Library of Medicine providing high quality information about marketed drugs, including their FDA labels (package inserts) for more than 54,000 drugs;

(iv) of the U.S. FDA; and

(v) of MIMS, a popular and well-respected publication of drug references in the Philippines, the U.S. and other countries.

(3) Philippine National Drug Formulary, *Essential Medicines List,* Volume 1, 7th Edition, 2008, published by The National Formulary Committee, National Drug Policy-Pharmaceutical Management Unit 50, Department of Health, Manila, Philippines.

(4) Leading published learned treatises and studies accessed from and through:

(i) the University of Santo Tomas (UST) Library (Miguel de Benavides Library), as duly certified by Kaori B. Fuchigami, the Reference Librarian;

(ii) the Makati Medical Center Medical Library, as duly certified by Ma. Ana Patricia H. Alvia, a Medical Consultant of the Department of Obstetrics and Gynecology of the Makati Medical Center, Makati City, and the Head of the Bioethics Committee of the Makati Medical Center, Department of Obstetrics and Gynecology;

(iii) various indicated websites; and

(iv) personal online subscription.

(5) Medical Textbooks used by medical schools here and abroad:

(i) The *Textbook of Obstetrics, 3rd Edition (Physiologic and Pathologic Obstetrics), Copyright 2008,* published by the Association of Writers of the Philippine Textbooks of Obstetrics and Gynecology, Inc.;

(ii) *Williams Obstetrics, 23rd Edition, Copyright 2010,* published by The McGraw-Hill Companies, Inc.;

(iii) *Comprehensive Gynecology, 5th Edition, Copyright 2007,* published by Mosby, an affiliate of Elsevier Inc.; and

(iv) *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (12 ed.), *Copyright 2010,* published by Mcgraw-Hill. Medical Publishing Division.

(6) Reference Textbook: *A Consumer's Guide to the Pill and Other Drugs* by John Wilks B. Pharm. M.P.S., 2nd Edition, published by ALL Inc., Stafford, Virginia 22555.

(7) Other duly identified Reference Textbooks.

All the above, which we will present, identify, quote from, refer to and rely upon in the course of our Opposition are credible and reliable evidence pursuant to Sections 46 and 49 of Rule 130, Sections 19, 24 and 25 of Rule 132 of the Rules of Court, and Rules 3, 4 and 5 of the Rules on Electronic Evidence.

8. Attachments to the Opposition:

Volume 1. We have prepared a Summary of Relevant Information about the Combined Oral Contraceptives and the

Progestin-Only Contraceptives in table-format. This is compiled and bound in Volume 1, together with printed copies of the supporting reference materials with relevant portions duly marked and highlighted.

Volume 2. We have printed copies of the supporting reference materials mentioned in Section 8(4) above, indicating the sources.

2. Are Hormonal Contraceptives, Intrauterine Devices, And Injectables Abortifacients?

2.1 How do Contraceptives Work? Mechanisms of Action of Hormonal Contraceptives. The Primary Mechanism is Contraceptive, and the Secondary Mechanism is Abortive.

When we talk of "Hormonal Contraceptives" we refer to "hormonal methods of contraception" and the currently available preparations are the combined estrogen-progestin formulation and the progestin-only formulation. The available hormonal contraceptives are the combined oral contraceptives (COCs), progestin-only pills, patch, long-acting progestin injectables, progestin implants and combined injectable contraceptives. The COCs are the most frequently used method of hormonal contraception.[1]

The ***Textbook of Obstetrics, 3rd Edition (Physiologic and Pathologic Obstetrics), Copyright 2008,*** published by the Association of Writers of the Philippine Textbooks of Obstetrics and Gynecology, Inc.[2], ***Williams Obstetrics, 23rd Edition, Copyright 2010,*** published by The McGraw-Hill

[1] The ***Textbook of Obstetrics 3rd Edition (Physiologic and Pathologic Obstetrics), Copyright 2008,*** published by the Association of Writers of the Philippine Textbooks of Obstetrics and Gynecology, Inc., pp. 1022-1023.

[2] page 1023.

Companies, Inc.[3], and ***Comprehensive Gynecology, 5th Edition, Copyright 2007,*** published by Mosby, an affiliate of Elsevier Inc.[4] – well-recognized medical textbooks used by medical schools in the Philippines and all over the world, mention that the combined estrogen-progestin formulation and the progestin-only formulation have the following multiple mechanisms of action that contribute to their high effectiveness:

(a) The foremost action is inhibition of ovulation, although not consistently;

(b) The progestins make the cervical mucus thick, viscid and scanty thereby retarding and impairing sperm transport and penetration. They also alter motility of the uterus and oviduct, thus impairing transport of both ova and sperm;

(c) Furthermore, they alter the endometrium so that its glandular production of glycogen is diminished, and less energy is available for the blastocyst to survive in the uterine cavity. In short, they render the endometrium unfavorable for implantation.

The progestin produces a decidualized endometrial bed with exhausted and atrophied glands while estrogen produces areas of edema alternating with portions of dense cellularity.

The formulations cause alterations to the lining of the womb converting the proliferative nature of the endometrium to a secretory endometrium, which is a thin, devasculating lining, physiologically unreceptive to receiving and sustaining a human embryo. In many medical text books, this action is referred to as 'the inhibition of nidation' (Latin *nidus* nest).

The first two mechanisms [(a) and (b)] are true contraception because they prevent fertilization and hence, there are no fertilized ova formed. When the first two mechanisms of action fail, and scientific findings point to such failure as will be discussed below, there is the third and back-

[3] page 673.

[4] page 284.

up mechanism [(c)] which is abortifacient in nature because it prevents the implantation of the fertilized ovum in the uterus. This third mechanism of action is also referred to in medical literature as the ***post-fertilization effect.***

While the initial or primary mechanism of hormonal contraceptives may be the prevention of fertilization, its uterine thinning mechanism is likewise established, making the uterus inhospitable to the implantation of the fertilized ovum. It is through this thinning action that the hormonal contraceptives act to cause chemical or induced abortion.

2.2 Post-Fertilization Effect. The post-fertilization effect of oral contraceptives could involve any 1 or more of the following 3 actions:[5]

2.2.1 A post-fertilization pre-implantation effect would consist of a **slower transport of the pre-embryo through the fallopian tube, preventing the pre-embryo from implanting in the uterus**; this could result either in the **unrecognized loss of the pre-embryo or in an ectopic (tubal) pregnancy if the pre-embryo had slower tubal transport and ended up implanting in the fallopian tube.**

2.2.2 A peri-implantation effect would be the alteration of the endometrium such that a **pre-embryo that reaches the uterus is unable to successfully implant into the endometrial lining of the uterus**.

2.2.3 A post-implantation effect could result from alteration of the endometrium not sufficient to prevent implantation **but unfavourable for maintenance of the pregnancy**; a pre-embryo or embryo already implanted in the endometrial lining of the uterus would be unable to maintain itself long enough to result in a clinically recognized pregnancy.

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[5] *Postfertilization Effects of Oral Contraceptives and Their Relationship to Informed Consent,* **Walter L. Larimore, MD; Joseph B. Stanford, MD, MSPH**, ARCH FAM MED/Vol. 9, February 2000. (Vol. 2).

2.3 Endometrial Thickness and Implantation. The medical literature indicates that there is a critical thickness of the endometrium needed to sustain implantation of a human embryo. Endometrial thickness has long been used as a marker of adequate receptivity of the uterus and as a prognostic factor in embryo transfers. Several studies suggest that pregnancy is less likely when the endometrium is <8mm. Endometrial thickness <8mm does not exclude the possibility of pregnancy, but it is less optimal.[6]

Several studies on the effect of pills on endometrial thickness which hampers embryo implantation were cited and discussed by John Wilks, B. Pharm. MPS MACPP:[7] Isaacs *(Fert Steril 1996)* reported that an endometrial thickness of at least 10mm or more, around the time of ovulation, 'defined 91% of conception cycles'. 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. Shoham *(Fert Steril, 1991)* reported that a mid-luteal thickness of 11mm 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'.

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'. 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

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[6] *A retrospective cross-sectional study: fresh cycle endometrial thickness is a sensitive predictor of inadequate endometrial thickness in frozen embryo transfer cycles,* **Patricia T. Jimenez, Samantha B. Schon, Randall R. Odem, Valerie S. Ratts and Emily S. Jungheim**, REPRODUCTIVE BIOLOGY AND ENDOCRINOLOGY 2013. (Vol. 2).

[7] *The Impact of the Pill on Implantation Factors—New Research Findings,* **John Wilks, B. Pharm.** MPS MACPP, ETHICS & MEDICINE (2000) 16.1. (Vol. 2).

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 but they failed to develop a median endometrial thickness in excess of 6mm. To recall, follicles of this size are 'thought to be associated with increased risk of escape ovulation'.

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.

2.4 The Process of Implantation. John Wilks gave a very clear and illustrative explanation of the process of implantation and stated that:[8] The process of implantation of the human embryo into the lining of the womb is a very complex and delicate process. Proper attachment and successful implantation is under the guidance and control of a vast array of 'implantation factors'. These chemical factors actually cause what is referred to in medical journals as "cross-talk" between the embryo and the cells which line the womb. That is, the cells of the new human embryo and the cells of the lining of the womb chemically speak to each other. The purpose of this chemical communication is so the womb will be fully prepared and ready to bind with the human embryo when it attempts to implant.

The oral contraceptives' role in all of this is that it alters the levels of these implantation factors. Too much estrogen and progesterone, via the pill, causes harmful changes to the levels of these implantation factors. Recent research has shown that implantation fails if the levels of estrogen and

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8 *The Impact of the Pill on Implantation Factors—New Research Findings,* **John Wilks, B. Pharm.** MPS MACPP, ETHICS & MEDICINE (2000) 16.1. (Vol. 2).

progesterone are too high.

It is because the levels of these two hormones are wrong that the week-old embryo cannot attach to the womb. Cell-talk fails, the proper development of the womb does not occur, and the embryo dies from a lack of nutrition normally supplied to it from the lining of the womb. In fact, wrong levels of artificial progesterone have been shown to cause a very thin lining of the womb, making implantation impossible.

This concept can be understood more fully by considering the example of a space shuttle, low on fuel and oxygen, which urgently needs 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. If this electronic communication fails—disrupted "cell-talk"—, the shuttle may go to the wrong docking bay, fail to attach to the mother ship, drift away, and the crew dies from a lack of food and oxygen. Or it might go to the right bay but not find all the docking apparatus in place. Again, the attachment between the two fails due to faulty communication and the crew dies.

As well, there are a special group of molecules found both on the lining of the womb and on the 7-8 day old human embryo known as integrins. Integrins are referred to as 'adhesion molecules'. Researchers have shown that these adhesion molecules greatly assist the process of implantation.

Going back to our example of the docking process between a space shuttle and the mother ship, integrins could be thought of as grappling hooks that 'hold' the human embryo onto the womb whilst the process of implantation is completed. The artificial hormones in the pill have been shown to damage the ability of integrins—the implantation 'hooks'—to function properly. Because of this damage to the proper functioning of integrins, the limited amount of time the human embryonic person has for attaching, known as the 'window of implantation', is closed. As a result, the human embryonic person dies.

As shown, the pill acts as the great communication wrecker.

On the various implantation factors, John Wilks likewise gave a thorough explanation in the same scholarly article and in his book, *A Consumer's Guide to the Pill and Other Drugs, 2nd Edition, Chapter One. The Pill: How it Works and Fails.*[9]

2.5 Breakthrough Or Escape Ovulation. Contraceptive Mechanisms Sometimes Fail And Ovulations Occur, And Abortifacient Mechanism Provides The Back-Up Action.

John Wilks also discussed the 'breakthrough or escape ovulation in this wise:

In varying degrees, the various formulations of hormonal contraceptives act by suppression of ovulation. However, neither the progesterone-only formulation nor the combined formulation always inhibits ovulation and cases of **'break-through ovulation' or 'escape-ovulation'** have been reported. As the name suggests, a woman ovulates even though she always takes her daily dose of the pill, is not sick, and is not taking any other medications.

The pioneering research in this area was done by Dr. Nine Van der Vange, State University of Utrecht, Department of Obstetrics & Gynecology. The following citation is instructive:

> The advent of ultrasound technology allowed for careful monitoring of ovarian function in women using OC's [oral contraceptives]. In contrast to earlier assumptions, women were found to have varying degrees of residual ovarian activity, which is characterised by follicular development and concurrent plasma [blood] oestradiol levels.

Other researchers using this same ultrasound approach have reported break-through ovulation. Grimes and co-workers (1994) stated, **"...suppression of follicular development is incomplete with the contemporary low-**

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9 Pp. 1-11

dose pill." In fact, this study reported a rate of break-through ovulation of 26.7 ovulations per 100 woman-years. Other studies have reported higher rates. This is not the only report of break-through (or escape) ovulation.

Coney and DelConte (1999) have published further substantive evidence of the abortifacient capacity of the COCP [combined oral contraceptive pill]. They reported that in a study of 26 healthy taking Alesse® (100 □g levonorgestrel, 20 □g ethinyl estradiol), ovulation was confirmed in 2.7% of women.

Given that there were 2 ovulations during 3 cycles of treatment for these 26 women, the ovulation rate is 50 per 100-women years. Importantly, **"the ovulations that occurred did not appear to be due to noncompliance** [by the women], **based on our review of patient pill diaries and returned pill packages."** This means that patient compliance was high, and the ovulations detected where attributable to a 'failure' of the pill to completely suppress ovulation.

Other factors that contribute to the failure of the contraceptive mechanisms of action are:

Some women forget to take a tablet each day. Missing a single tablet may be all that is needed for ovulation to occur. Even the drug companies agree that missing a single dose is significant. Ovulation may occur, which could lead to a diagnosed pregnancy. That is why the leaflet inside the pill packet recommends using something like a condom or diaphragm, even if you are only 12 hours late in taking your daily pill tablet. The pill manufacturers also suggest that a condom or diaphragm should be used for seven days because of the risk of ovulation and pregnancy.

Another reason some women have a diagnosed pregnancy while on the pill can be due to stomach illness such as vomiting or diarrhea. These illnesses may prevent the full dose of the pill being absorbed into the woman's body. The effect of less-than-complete drug absorption is the same as missing a dose - ovulation could occur. Again, the pill manufacturer recommends condom or diaphragm use for a full 7 days to prevent sperm and ovum joining.

A third reason for a diagnosed pregnancy whilst taking the pill could be because of a drug interaction with antibiotics (such as amoxycillin, co-trimoxazole, tetracycline, erythromycin and amphotericin), or large doses of vitamin C, or anti-epileptic medication, barbiturates and rifampicin (used for T.B.). The effect of the drug interaction is to reduce the quantity of hormones absorbed. Therefore, ovulation might occur.

Walter L. Larimore, MD and Joseph B. Stanford, MD, MSPH also discussed about breakthrough ovulation**:**[10]

Breakthrough ovulation rates vary by the form and the dose of the oral contraceptives (OCs) used. With OCs, breakthrough ovulation is more likely with lower doses of estrogen and with imperfect rather than perfect use. *Perfect use* of OCs implies taking them consistently and correctly (i.e. in the correct order, on time, each and every day, and without other medications that might diminish its effectiveness of OCs). *Typical use* is described as the full range of usage patterns for OCs that actually occurs in women. While some smaller numbers of women for 6 or fewer cycles have reported breakthrough ovulation rates of near 0, studies that evaluated women for at least 6 cycles demonstrated ovulation rates ranging from 1.7% to 28.6% per cycle. For progesterone-only pills (POPs), reported breakthrough ovulation rates range from 33% to 65%.

Obviously, breakthrough ovulation can result in unintended pregnancy.

2.6 Evidence for Post-Fertilization Effects. Some say that there is no direct evidence for the abortifacient character of the hormonal contraceptives and that the indirect evidence for such a position is inconclusive and/or negligible. Experts are agreed that there is no direct evidence that the hormonal contraceptives cause abortions. And if their post-fertilization effects were studied directly, it would either involve techniques

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[10] *Postfertilization Effects of Oral Contraceptives and Their Relationship to Informed Consent,* **Walter L. Larimore, MD; Joseph B. Stanford, MD, MSPH**, ARCH FAM MED/Vol. 9, February 2000. (Vol. 2).

and procedures that are immoral by virtue of destroying early embryonic life or involve studies that would be moral but non-definitive since they would include indicators such as the Early Pregnancy Factor (EPF) (a pregnancy-associated immunosuppressive protein detected in maternal sera by rosette inhibition assay that, to date, provides a less than acceptable accuracy index). There is however indirect evidence that post-fertilization effects play a role in loss of embryonic life induced by the hormonal contraceptives.

Walter L. Larimore, MD and Joseph B. Stanford, MD, MSPH did an analysis of the evidence available and came up with a grade for the available evidence using a standard quality of evidence table. The analysis and the findings are set forth below:[11] ---

2.6.1 Method of Study Used by Authors.

The authors' analysis of the evidence involved a review of the abstracts of all studies of OCs published since 1970 available on MEDLINE that discussed the commonly used OCs, including low-dose (<50 ug of estrogen) phasic combined oral contraceptives (COCs), low-dose monophasic-only pills [POPs]). They also reviewed the patient handouts provided by OC manufacturers and the most recent editions of several medical textbooks and reference books.

Since there is variability in the definitions and use of terminology in reproductive medicine, the authors used the American Academy of Obstetrics and Gynecology Committee on Ethics' definition for *fertilization, implantation, embryo and preembryo. Preembryo* is a general term that includes the human development stages that occur after fertilization but prior to the appearance of the primitive streak about 14 days after fertilization. From that point until the end of the eighth week after fertilization, the term *embryo* is used. Implantation is the process whereby the preembryo attaches to the endometrial lining of the uterus. This process begins 5 to 7

[11] *Postfertilization Effects of Oral Contraceptives and Their Relationship to Informed Consent,* **Walter L. Larimore, MD; Joseph B. Stanford, MD, MSPH**, ARCH FAM MED/Vol. 9, February 2000. (Vol. 2).

days after fertilization and may last several days. For the review, they defined *postfertilization effects* to include mechanisms of action that operate after fertilization to prevent a clinically recognized intrauterine pregnancy. They looked specifically for studies referencing any postfertilization effects of OCs. When many studies indicated similar findings, they listed the most recent or most methodologically sound references on other systematic or general reviews of particular subjects.

Three (3) lines of evidence have been suggested to support the hypothesis that 1 or more post-fertilization effects are operative in at least some women taking oral contraceptives. Using a standard quality of evidence table **(Table)**, the authors graded the available evidence.

Quality of Evidence

Excellent	**I**	Evidence obtained from at least one properly randomized controlled trial.
Very good	**II.1**	Evidence obtained from well-designed controlled trials without randomization.
Good to Very Good	**II.2**	Evidence obtained from well-designed cohort or case-controlled analytic studies, preferably from more than one center or research group.
Good	**II.3**	Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence.
Poor to Good	**III**	Opinion of respected authorities based on clinical experience, descriptive studies and case reports, or reports of expert committees.

2.6.2 Evidence For Endometrial Changes That May Affect Endometrial Receptivity.

Oral contraceptives directly affect the endometrium. These effects have been presumed to render the endometrium relatively inhospitable to implantation or to the maintenance of the preembryo or embryo prior to clinically recognized pregnancy by producing a predecidual or decidualized endometrial bed with diminished thickness and with widely spaced, exhausted and atrophied glands by altering the cellular structure of the endometrium leading to the production of areas of edema alternating with areas of dense cellularity, and by altering the biochemical and protein composition of the endometrium.

Although these changes are consistently seen in women taking OCs, there is currently no direct evidence to link these changes to pre-embryo or embryo loss in women taking OCs. However, this hypothesized postfertilization effect seems to be so well-accepted that in many medical articles and textbooks it has been explicitly listed as the third mechanism of OCs (after suppressing ovulation and prefertilization effects.) For example, the Food and Drug Administration approved product information for OCs in the *Physicians' Desk Reference* states:

> Although the primary mechanism of this action is inhibition of ovulation, other alterations include damage in the cervical mucus, which increases the difficulty of sperm entry into the uterus, and changes in the endometrium, which reduce the likelihood of implantation.

An independent clinical pharmaceutical reference also contains this assertion. **Larimore and Stanford considered this level III (Poor to Good) evidence (Table)**.

To assess the clinical significance of an altered endometrium, it was helpful to examine data that compared endometrial thickness with the receptivity of the endometrium to postembryos during in vitro fertilization procedures. Magnetic resonance imaging scans of the uteri of women reveal that the OC users have endometrial linings that are consistently thinner than the endometrial linings of nonusers

up to 58% thinner. Of the first ultrasound studies published, the first did not find a relationship between endometrial thickness and in vitro fertilization implantation rates, however, subsequent studies noted a trend, and one demonstrated that a decreased thickness of the endometrium decreased the likelihood of implantation. Larger, more recent studies all concluded that endometrial thickness is related to the functional receptivity of the endometrium. Furthermore, when the endometrial lining becomes too thick, then implantation does not occur. The minimal endometrial thickness required to maintain a pregnancy in patients undergoing in vitro fertilization has been reported, ranging from 5 mm, to 9 mm, to 13 mm, whereas the average endometrial thickness in women taking OCs is 1.1 mm. These data would seem to lend credence to the Food and Drug Administration-approved statements that "… changes in the endometrium… reduce the likelihood of implantation." **Larimore and Stanford considered this level II.2 (Good to Very Good) evidence. (Table).**

2.6.3 Evidence For Integrin Changes Affecting Fallopian Tube and Endometrial Receptivity for Implantation.

Integrins are a family of cell adhesion molecules that are accepted as markers of uterine receptivity for implantation." Temporal and spatial expression of these endometrial peptides is believed to contribute to the establishment and maintenance of a cyclical endometrial receptivity. Three cycle-dependent integrins (∞1□1, ∞4□1, ∞V□3) have been shown to be "… coexpressed apparently only for a brief interval of the cycle that corresponds with the putative window of maximal uterine receptivity" and "… have emerged as reliable markers of normal fertility." Of these three, the ∞V□3 integrin seems "to be an excellent marker to study the molecular events leading to the establishment of uterine receptivity and successful implantation." These three integrins are conspicuously absent in the endometrium of most patients with luteal phase deficiency, endometriosis and unexplained infertility.

In addition, integrin expression is significantly changed

by OCs. Integrins have been compared using endometrial biopsy specimens from normally cycling women and women taking OCs. In most OC users, the normal patterns of expression of the integrins are grossly altered, leading Somkuti et al to conclude that the OC-induced integrin changes observed in the endometrium have functional significance and provide evidence that reduced endometrial receptivity does indeed contribute to the contraceptive efficacy of OCs. They hypothesized that the sex steroids in OCs alter the expression of these integrins through cytokines and therefore predispose to failure of implantation or loss of the preembryo or embryo after implantation**. Larimore and Stanford considered this level II.3 (Good) evidence (Table).**

Integrins have also been identified in the fallopian tube. Of interest, the □V subunit is expressed in the fallopian tube epithelium throughout the cycle, but the □3 subunit is only upregulated during the period of endometrial receptivity. Therefore, it has now been postulated that the normal tubal epithelium also has an implantation window that "…affords the opportunity for trophoblast attachment should a 5-7 day preembryo be unduly retained in the tube." As discussed earlier, one of the postulated actions of the OCs is a slowing of tubal peristalsis (via smooth muscle relaxation); therefore, a reduction in tubal peristalsis that is associated with an upregulation of the □V□3 integrin in the epithelium of the fallopian tube could theoretically lead to an increased risk of ectopic pregnancies in women taking OCs.

If breakthrough ovulation occurs while using the COC, then to some extent ovarian and blastocyst steroidogenesis could theoretically "turn on" the endometrium, causing it to normalize prior to implantation in the ovulatory cycle. However, after discontinuing use of COCs, it usually takes several cycles for a woman's menstrual flow to approach the volume of women who have not taken hormonal contraception, suggesting that the endometrium is slow to recover from its COC-induced atrophy. Furthermore, in women who have ovulated secondary to missing 2 low-dose COCs, the endometrium in the luteal phase of the ovulatory cycle has been found to be nonsecretory.

2.6.4 Increased Extrauterine Pregnancy to Intrauterine Pregnancy Ratio.

If the action(s) of OCs on the fallopian tube and endometrium were such as to have no postfertilization effects, then the reduction in the rate of intrauterine pregnancies in women taking OCs should be proportional to the reduction in the rate of extrauterine pregnancies in women taking OCs. If the effect of OCs is to increase the extrauterine-to-intrauterine pregnancy ratio, this would indicate that one or more postfertilization effects are operating. All published data that Larimore and Stanford could review indicated that the ratio of extrauterine-to-intrauterine pregnancies is increased for women taking OCs and exceeds that expected among control groups of pregnant women not currently using OCs. These case controlled series come from 33 centers in 17 countries and include more than 2800 cases and controls. The odd ratios in these studies ranged from 1.7 (95% confidence interval [C1], 1.1-2.5) to 1.8 (95% C1, 0.9-3.4) to 4.3 (95% C1, 1.5-12.6) to 4.5 (95% C1, 2.1-9.6) to 13.9 (95% C1, 1.8-108.3). The letter by Job-Spira et al seems to represent the same data set of 279 cases and controls as the study by Coste et al. The meta-analysis by Mol et al includes 2 of the publications, but one of these may include women taking POPs. Therefore, of the 5 publications, only 2 allow review of the association of COCs with ectopic pregnancy. These two studies from 7 maternity hospitals in Paris, France, and 3 in Sweden involved 484 women with ectopic pregnancies and 289 pregnant controls and suggest that at least some protection against intrauterine pregnancy is provided via postfertilization preimplantation effects. It was recognizes that studies that have used nonpregnant controls have not shown a risk of increased ectopic pregnancy for users of COCs. In their review, they restricted their analysis to studies using pregnant controls, because they concur with researchers in this field that "... when considering the situation where a woman became pregnant during contraceptive use, one should focus on pregnant controls." Therefore, COC use seems to be associated with an increased risk of ectopic implantation or unrecognized loss of preembryos. **Larimore and Stanford considered this level II.2 (Good to Very Good) evidence (Table).**

Ectopic pregnancy is a particular form of postfertilization loss that involves substantial risks to the woman, and thus the absolute risk of ectopic pregnancy for women taking OCs will be of interest to clinicians and patients. Converting a relative risk of ectopic pregnancy to an absolute risk has many

inherent difficulties that have been reviewed elsewhere. Nevertheless, adapting the method suggested by Franks et al would allow one to predict that the ectopic pregnancy rate for women taking OCs would be the product of 3 factors: (1) the overall pregnancy rate per 1000 woman-years among those taking OCs, (2) the proportion of extrauterine pregnancies compared with all pregnancies for a comparable control population not taking OCs and (3) the relative risk for ectopic pregnancy in women taking OCs compared with the control population, which may be estimated by the odds ratio from case-control studies. For factor 1, Potter suggests 40 for good compliers and 80 for poor compliers. For factor 2, the proportion of ectopic pregnancies in the 1990s is estimated to range from 1 in every 56 to 64 pregnancies (0.0156 to 0.0179). A reasonable range for factor 3 would be 1.1 to 13.9, based on the studies discussed above. This model would predict an absolute risk ranging from 0.7 (40 x 0.0156 x 1.1) to 19.9 (80 x 0.0179 x 13.9) ectopic pregnancies per 1000 woman-years. We could only find one study, from Zimbabwe, which reported an absolute risk of ectopic pregnancy in women taking OCs of 0.5 per 1000 woman-years.

The risk of ectopic pregnancy is higher with POPs, and ectopic pregnancy has been discussed at length by a number of investigators as a clinically significant potential complication of POPs. The odds ratio of an extrauterine pregnancy for a woman taking a POP (compared with pregnant controls) was reported in only one study and was 79.1 (95%C1, 8.5-735.1). Assuming an overall clinical pregnancy rate of 30 to 70 per 1000 woman-years, this equates to a predicted absolute risk of 4 to 99 ectopic pregnancies per 1000 woman-years (130 or 70) x [0.0156 or 0.0179] x [8.5 or 79.1] in women taking POPs. This is reasonably concordant with absolute rates of ectopic pregnancy in women taking POPs, which have been reported to range from about 3 to about 20 per 1000 woman years.

Data from case-controlled series demonstrate that women with clinically recognized pregnancy are no more or less likely to miscarry based on whether they were taking an OC after their pregnancy was clinically recognized. However, the epidemiology, biology and recognized risk factors of clinically recognized embryo or fetal loss (spontaneous abortion after clinically recognized pregnancy) do not seem to apply to early (unrecognized) pre-embryo or embryo loss, as

the available evidence suggests that the mechanisms of early establishment and maintenance of pregnancy and later maintenance of pregnancy are qualitatively and substantially different.

2.6.5 Summary Of Evidence: All Evidence Support The Possibility Of Post-Fertilization Effects. And Medical Literature Does Not Support The Hypothesis That Post-Fertilization Effects of OCs Do Not Exist.

The **evidence supporting post-fertilization effects** for OC's in the prevention of clinically recognized pregnancy **ranges from poor (level III) to very good (level II.2).** Specifically, **evidence based on alterations in endometrial biochemistry and histology (level III), evidence based on endometrial thickness and endometrial receptivity from research studying in vitro fertilization (level II.2), and evidence based on endometrial integrins (level II.3) all support the possibility of peri-implantation or post implantation effects.** Furthermore, **evidence based on ectopic-to-intrauterine risk ratios from multiple case-control studies (level 11.2) supports the possibility of post-fertilization preimplantation, peri-implantation, or post implantation effects. However, we could identify few data that would assist in quantifying these postfertilization effects. It seems likely that for perfect use of COC's, postfertilization mechanisms would be likely to have a small but not negligible role. For POPs, COCs with lower doses of estrogen, and imperfect use of any OCs, postfertilization effects are likely to have an increased role. In any case, <u>THE MEDICAL LITERATURE DOES NOT SUPPORT THE HYPOTHESIS THAT POSTFERTILIZATION EFFECTS OF OCS DO NOT EXIST.</u>**

Despite the evidence, which suggests that postfertilizatiopn effects for OCs are operational at least some of the time, and the fact that a postfertilization mechanism for OCs is described in the *Physicians' Desk Reference,* in *Drug Facts and Comparisons,* and in most standard gynecologic, family practice, nursing, and public health textbooks, it was anecdotally found that few physicians or patients are aware of this possibility. Therefore, the authors believe that the

potential for postfertilization effects is probably not routinely presented to patients as part of their informed consent to use an OC. Furthermore, it is of concern to the authors that only one of the many OC patient information handouts they and others have reviewed, including those produced by the OC manufacturers, mentions the possible postfertilization mechanism, despite the fact that this information is nearly always included in the professional labeling of these same OCs.

Since there is evidence to support the existence of postfertilization effects and because it is impossible to know in advance which patients would find the potential for this effect objectionable, the authors believe that that the lack of information regarding postfertilization effects in patient information materials about OCs represents a potential failure to provide complete informed consent. Furthermore, if this mechanism of an OC violates the moral requirements of a woman, then failure to disclose this information seriously jeopardizes her autonomy. If information about the mechanism of an OC is deliberately withheld or misstated, then an unethical deception occurs. Failure to disclose information that might lead a patient to choose a different method of treatment is generally considered to be unethical. Therefore, it seems clear to that failure to inform patients of a possible postfertilization mechanism of an OC is a failure to provide informed consent

2.7 CONCLUSION: **THERE IS NO SCIENTIFIC PROOF THAT THE ORAL CONTRACEPTIVES DO NOT HAVE AN ABORTIFACIENT EFFECT, BUT THERE IS SCIENTIFIC PROOF THAT THE ORAL CONTRACEPTIVES POSE A POSSIBLE CAUSE OF DEATH TO THE UNBORN CHILD.**

The available evidence supports the hypothesis that when ovulation and fertilization occur in women taking oral contraceptives, post-fertilization effects are operative on occasion to prevent clinically recognized pregnancy or to cause induced abortion. **TO DATE, THERE IS NO SCIENTIFIC PROOF THAT THE ORAL CONTRACEPTIVES DO NOT HAVE AN ABORTIFACIENT EFFECT, BUT THERE IS SCIENTIFIC PROOF THAT THE ORAL CONTRACEPTIVES POSE A POSSIBLE CAUSE OF DEATH TO THE UNBORN CHILD.**

3. Intrauterine Contraceptive Devices (IUDs) Are Abortifacients.

3.1 Post-fertilization Effects of IUDs. There are many potential mechanisms of action for the intrauterine device (IUD), which vary by type of IUD (inert, copper, or hormonal). In the scholarly paper of Joseph B. Stanford, MD, MSPH, and Rafael T. Mikolajczyk, MD, they discussed about the reviews they conducted on the evidence for each potential mechanism of action of IUD.[12] They concluded after a rigorous examination that the evidence on the mechanism of action of IUDs indicates that both pre-fertilization and post-fertilization effects are significant contributors to the clinical efficacy of all types of IUDs. Although pre-fertilization effects are more prominent for the copper IUD, both pre-fertilization and post-fertilization mechanisms of action contribute significantly to the effectiveness of all types of intrauterine devices. **AND THE POST-FERTILIZATION MECHANISMS OF ACTION OF THE IUD INCLUDE THE FOLLOWING: (1) SLOWING OR SPEEDING THE TRANSPORT OF THE EARLY EMBRYO THROUGH THE FALLOPIAN TUBE; (2) DAMAGE TO OR DESTRUCTION OF THE EARLY EMBRYO BEFORE IT REACHES THE UTERUS; AND (3) PREVENTION OF IMPLANTATION.**

Another scholarly paper evaluated the available evidence for the mechanisms of action of copper-impregnated IUDs. Joseph A. Spinnato II, MD summarized his analysis as follows: **(1) THE AVAILABLE EVIDENCE SUPPORTS A CONTINUED SIGNIFICANT ROLE FOR A POST-FERTILIZATION MECHANISM OF ACTION OF IUDS; (2) THERE IS LITTLE COMPELLING EVIDENCE TO SUGGEST THAT COPPER-BEARING IUDS RELIABLY ELIMINATE THE LIKELIHOOD OF FERTILIZATION; (3) Because it is reasonable to assume that many patients would object to IUDs if informed of**

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[12] *Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects,* **Joseph B. Stanford , MD, MSPH, and Rafael T. Mikolajczyk, MD,** AM J OBSTE GYNECOL, Volume 187, Number 6 (December 2002). (Vol. 2).

their post-fertilization mechanism of action and it is difficult to accurately predict which patients would object, a discussion of this mechanism of action is necessary for adequate informed consent for UD use.[13]

4. Injectables Are Also Abortifacients.

4.1 ***Mechanism of Actions.*** **---** The mechanisms of action of injectable progestin contraceptives are multiple and include ovulation inhibition, increased cervical mucus viscosity, and **CREATION OF AN ENDOMETRIUM UNFAVORABLE FOR OVUM IMPLANTATION.** [14]

5. Emergency Contraceptives Are Also Abortifacients.

Emergency contraception provides women with a last chance to prevent unwanted and unintended pregnancy after unprotected sexual intercourse, including sexual assault. Current methods of emergency contraception include combined oral contraceptives (COCs, progestin-only products, copper-containing IUDs, and mifepristone.

5.1 *Effects On Implantation*[15]

The COC regimens are more effective the sooner they are

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[13] *Mechanism of action of intrauterine contraceptive devices and its relation to informed consent,* **Joseph A. Spinnato II, MD,** AM J OBSTET GYNECOL, Volume 176, Number 3 (March 1997). (Vol. 2).

[14] Williams Obstetrics, Cunningham, Leveno, Bloom, Hauth, Rouse, Spong, 23rd Edition, copyright 2010, The McGraw-Hill Companies, Inc., pp. 692-693.

[15] *Postfertilization Effect of Hormonal Emergency Contraception,* **Chris Kahlenborn, Joseph B. Stanford, and Walter L. Larimore,** The Annals of Pharmacotherapy, 2002 march, Volume 36. (Vol.2).

taken after unprotected intercourse. The first dose is taken ideally within 72 hours of intercourse but may be given up to 120 hours. The initial dose is followed 12 hours later by a second dose. Emergency hormonal contraceptive regimens are highly effective and decrease the risk of pregnancy by up to 94 percent (American college of Obstetricians and Gynecologists, 2005a).[16] Studies indicate that the efficacy of emergency contraceptives shows that they do more than inhibit ovulation and other mechanisms are involved including the prevention of the implantation of the embryo.

For the progestin-only preparation, the major mechanism of action is inhibition or delay of ovulation, but other mechanisms include alteration of the endometrium, sperm penetration, and tubal motility.[17]

Chris Kahlenborn, Joseph B. Stanford, and Walter L. Larimore have come up with the following findings on the post-fertilization effects of hormonal emergency contraception:[18]

Oral Contraceptives (OCs) are known to adversely affect the implantation process. OCs affect integrins, a group of adhesion molecules that have been implicated as playing an important role in the area of fertilization and implantation. Somkuti et al. noted: **"These alterations in epithelial and stromal integrin expression suggest that impaired uterine receptivity is one mechanism whereby OCs exert their contraceptive action." In addition, prostaglandins are critical for implantation, but OC use lowers uterine prostaglandin concentrations. Finally, it is well known that OC use decreases the thickness of the endometrium as verified by magnetic resonance imaging scans, and a thinner endometrium makes implantation more difficult.** Because hormonal emergency contraceptive (EC) consists of hormones contained within OCs, it is possible that the use of hormonal EC has some of the same effects on the

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[16] Williams Obstetrics, Cunningham, Leveno, Bloom, Hauth, Rouse, Spong, 23rd Edition, copyright 2010, The McGraw-Hill Companies, Inc., pp. 692-693.

[17] *Ibid.*

[18] *Postfertilization Effect of Hormonal Emergency Contraception,* **Chris Kahlenborn, Joseph B. Stanford, and Walter L. Larimore**, The Annals of Pharmacotherapy, 2002 march, Volume 36. (Vol.2).

endometrium as does the use of OCs. A number of studies support this hypothesis, noting changes in endometrial histology, or uterine hormone receptor levels that persist for days after women used the Yuzpe regimen. All of these findings imply that use of the Yuzpe regimen unfavorably alters the endometrium.

In addition to the theoretical evidence that EC use adversely affects implantation, Hertzen and Van Look found that both use of the Yuzpe regimen and Plan B[19] reduced the expected number of pregnancies when they were used in the ovulatory phase (17–13 d prior to the next menstrual cycle) and postovulatory phase (13 d prior to the expected menstrual cycle), as well as in the preovulatory phase (as discussed earlier). In the groups that used the Yuzpe regimen in the ovulatory phase, 17 pregnancies occurred (54 were expected if EC was not used), whereas 7 occurred in the postovulatory phase (11 were expected). In the group that used Plan B, 7 pregnancies occurred (53 were expected) in the ovulatory phase, whereas 2 occurred in the postovulatory phase (10 were expected).

The above data are highly consistent with the hypothesis that hormonal EC has a postfertilization effect on the endometrium.

5.2 *Increased Risk of Ectopic Pregnancy?*[20]

One result of a post-fertilization effect of hormonal EC use might be an increased proportion of recognized pregnancies that are ectopic. If the actions of hormonal EC on the fallopian tube and endometrium were such as to have no postfertilization effects, then the reduction in the rate of intrauterine pregnancies (IUPs) in women taking agents used in EC should be proportional to the reduction in the rate of extrauterine pregnancies (EPs) in women using hormonal EC. However, if the effect of hormonal ECs is to increase the

[19] Yuzpe and Plan B are FDA-approved EC contraceptive methods in the US.

[20] *Postfertilization Effect of Hormonal Emergency Contraception,* **Chris Kahlenborn, Joseph B. Stanford, and Walter L. Larimore,** The Annals of Pharmacotherapy, 2002 march, Volume 36. – (Vol. 2).

EP/IUP ratio, this would indicate that one or more post-fertilization effects are operating.

The current proportion of clinical pregnancies that are ectopic is a little less than 2%. In the only study that the authors are aware of regarding hormonal EC and ectopic pregnancy, Kubba and Guillebaud noted that in 715 women who used the Yuzpe regimen, 17 pregnancies occurred, including 1 ectopic pregnancy (i.e., a 5.9% rate of ectopic pregnancy), supporting the possibility of one or more post-fertilization effects. However, the confirmation of a post-fertilization effect would take a much larger series of hormonal EC pregnancies to determine whether the proportion of ectopic pregnancies is indeed higher than in those not having used EC.

5.3 *Relative Contribution of Post-fertilization Effect*[21]

As noted earlier, 2 small studies have suggested that when EC is used before ovulation, ovulation may be inhibited in 55–75% of the cases. Under the highly optimistic assumption that hormonal EC use prevents ovulation in 87.5% of women treated, Trussell and Raymond estimated that a mechanism "other than preventing ovulation accounts for 13–38% of the estimated effectiveness of the Yuzpe regimen." This range is higher than 12.5% because hormonal EC is often used during or after ovulation when, by definition, mechanisms other than prevention of ovulation are in effect. **The most likely candidate for the mechanism "other than preventing ovulation" is a post-fertilization effect (by effects on the endometrium).**

5.4 *Summary and Implications: USE OF EC DOES NOT ALWAYS INHIBIT OVULATION EVEN IF USED IN THE PRE-OVULATORY PHASE, AND IT MAY UNFAVORABLY ALTER THE ENDOMETRIAL LINING REGARDLESS OF WHEN IN THE CYCLE IT IS USED.*

[21] *Ibid.*

The evidence to date supports the contention that use of EC does not always inhibit ovulation even if used in the preovulatory phase, and that it may unfavorably alter the endometrial lining regardless of when in the cycle it is used, with the effect persisting for days. The reduced rates of observable pregnancy compared with the expected rates in women who use hormonal EC in the preovulatory, ovulatory, or postovulatory phase are consistent with a postfertilization effect, which may occur when hormonal EC is used in any of these menstrual phases.

Emergency department protocols could also be impacted by evidence of a post-fertilization effect. For example, emergency departments of Catholic hospitals usually allow either no use of hormonal EC in their rape protocols or limited use (i.e., preovulatory use of hormonal EC). Catholic hospitals that do allow hormonal EC use prior to ovulation may wish to reassess their policies given the findings that EC use does not consistently stop ovulation and has the potential of causing a post-fertilization effect even when used prior to ovulation. Most large secular hospitals have fewer limitations on the use of hormonal EC as part of their rape protocols. Nevertheless, evidence of a post-fertilization effect from use of hormonal EC is important to physicians who must make a moral decision about prescribing or referring for a drug that can cause an early abortion.

6. *SUMMARY*
of Scientific Evidence and Technical Information on the Abortifacient and Adverse Effects of Hormonal Contraceptives, IUDs and Injectables.

6.1 Method. --- With the foregoing discussion and cited learned treatises and reference books and the additional available scientific and technical information from various sources as are going to be identified, we have scrutinized all the different hormonal contraceptives, IUDs and injectables sold in the Philippine market that have been approved by and registered with the Philippine Food and Drug Administration (FDA). We will determine whether or not they are abortifacient

by focusing on that part of the definition of Abortifacient under Section 4(a) of the RH Law which says: "induces …. the prevention of the fertilized ovum to reach and be implanted in the mother's womb" or the post-fertilization effects as discussed above. We have also noted the adverse effects, if any, of each brand.

We have summarized the various pieces of relevant information (from the Sources of Scientific and Technical Information) in a Table (Volume 1) which include the mechanisms of action and the adverse effects, if any, and the corresponding sources of information. We have listed all the Philippine FDA-registered contraceptives that are sold in the Philippine market by indicating their brand names as appearing in the FDA websites, old and new. We then grouped them into two (2) main groups: (1) the combined oral contraceptives, and (2) the progestin-only contraceptives. We further subdivided each group into the different formulations or generic names based on the active ingredients of each brand name. And then, based on the various sources of information, we make a conclusion whether each brand of hormonal contraceptive, IUD or injectable is Abortifacient according to the definition in Section 4(a) of the RH Law.

6.2 On The Abortifacient Nature Of Combination Hormonal Contraceptives. --- We grouped the brand names based on their active ingredients or generic names.

Shown below are the different generic groups with excerpts from the prescribing information and other technical write-ups which all point to the reduced likelihood of implantation of the fertilized ovum.

Keeping in mind the definition of "Abortifacient" in the RH Law, the pieces of information which specifically cite the effect of each generic type (based on active ingredients) of each brand of hormonal contraceptive, as well as IUD and injectable, on the uterine lining, are summarized below. For easy access and review, the internet links where these pieces of information can readily be verified are provided immediately after the generic name for each group.

The Table (Volume 1) also indicates the relevant information for each brand name, when available. We, however, will not be discussing them in this portion for the sake of brevity.

For the **Combined Oral Contraceptives (COCs)**, the generic groups are as follows:

(a) Ethinyl estradiol and levonorgestrel
http://www.drugs.com/mtm/ethinyl-estradiol-and-levonorgestrel.html

Ethinyl estradiol and levonorgestrel are forms of estrogen and progesterone, which are both female hormones involved in conception. ***Ethinyl estradiol and levonorgestrel are used together in this product as an emergency contraceptive (EC) to prevent pregnancy after contraceptive failure or unprotected intercourse.*** Ethinyl estradiol and levonorgestrel prevent ovulation (the release of an egg from an ovary), disrupt fertilization (joining of the egg and sperm), ***and inhibit implantation (attachment of a fertilized egg to the uterus)***.

(b) Ethinyl estradiol and desogestrel
http://www.drugs.com/mtm/apri.html

Ethinyl estradiol and desogestrel is a combination drug that contains female hormones that prevent ovulation (the release of an egg from an ovary). ***This medication also causes changes in your cervical mucus and uterine lining, making it harder for sperm to reach the uterus and harder for a fertilized egg to attach to the uterus.***

(c) Drospirenone and ethinyl estradiol
http://www.drugs.com/mtm/drospirenone-and-ethinyl-estradiol.html

Drospirenone and ethinyl estradiol prevent ovulation (the release of an egg from an ovary) and also cause changes in your cervical and ***uterine lining, making it harder for sperm to reach the uterus and harder for a fertilized egg to attach to the uterus.***

(d) Ethinyl estradiol and norgestrel
http://www.drugs.com/cdi/norgestrel-ethinyl-estradiol.html

Norgestrel/ethinyl estradiol is a combination birth control pill. It works by preventing ovulation, altering the cervical mucus, and ***changing the lining of the uterus.***

(e) Estradiol valerate and dienogest
http://www.drugs.com/cdi/estradiol-valerate-dienogest.html

Estradiol valerate and dienogest is a combination birth control pill. It works by preventing ovulation. It may also change cervical mucus to prevent the sperm from reaching the egg and ***change the lining of the uterus to prevent a fertilized egg from implanting in the uterus.***

(f) Gestodene and ethinyl estradiol.
http://www.mims.com/USA/drug/info/gestodene%20%2b%20ethinylestradiol/gestodene%20%2b%20ethinylestradiol?type=full&mtype=generic

The MIMS US website provides the following information: "Gestodene is a progestogen while ethinylestradiol is a synthetic oestrogen. Used together, they inhibit ovulation by suppressing the mid-cycle surge of luteinising hormone which causes changes in the cervical mucus, thus forming a barrier to sperm, ***and making the endometrium unreceptive to implantation."***

(g) Cypreterone acetate and ethinyl estradiol
http://www.mims.com.ph/PHILIPPINES/drug/info/Cybelle/?type=full

The MIMS Philippines website provides the following information on cyproterone and ethinyl estradiol, in its full information on "Cybelle", a brand of hormonal contraceptives which has these as its active ingredients. In the section "Mechanism of Action", the following words were found: "Cybelle also acts like an oral contraceptive, by preventing the release of eggs, thickening the mucus in the neck of the womb

to stop sperm passing through and ***making the lining of the womb unsuitable for an egg to grow on."***

(h) Norethisterone and ethinyl estradiol
http://www.mims.com/Philippines/drug/info/Micropil/Micropil-Micropil%20Plus?type=full

The MIMS Philippines website in the full prescribing information on Micropil and Micropil Plus, brands of norethisterone and ethinyl estradiol, in the Mechanism of Action section, states the following: "Although the primary mechanism of action is inhibition of ovulation, alterations in the genital tract including changes in the cervical mucus (which increase the difficulty of sperm penetration) and ***development of poor endometrial lining (which reduces the likelihood of implantation)*** may also contribute to contraceptive effectiveness.

(i) Ethinyl Estradiol + Levonorgestrel
http://www.drugs.com/cdi/levonorgestrel-ethinyl-estradiol.html
+ Ferrous Fumarate
http://www.idruginfo.com/?cat=drug&s=Femme&ingredient=Ethinyl%20Estradiol/Iron%20(Ferrous%20Fumarate)/Levonorgestrel

Levonorgestrel/ethinyl estradiol is a progesterone and estrogen combination birth control pill. It works by preventing ovulation, thickening the mucus in the cervix, and ***changing the lining of the uterus.***

Iron (ferrous fumarate) is for transport of oxygen to tissue and in cellular oxidation mechanism. It is used in preventing and treating iron-deficiency anemia.

(j) Etonogestrel + Ethinylestradiol
http://www.drugs.com/search.php?searchterm=ethinyl+estradiol%2Fetonogestrel

Ethinyl estradiol and etonogestrel contains female hormones that prevent ovulation (the release of an egg from an ovary). This medication also causes ***changes in your cervical mucus and uterine lining, making it harder for sperm to***

reach the uterus and harder for a fertilized egg to attach to the uterus.

(k) Norelgestromin + Ethinyl Estradiol 6mg/600mcg Transdermal Patch

http://www.drugs.com/mtm/ethinyl-estradiol-and-norelgestromin-transdermal.html

Ethinyl estradiol and norelgestromin contains a combination of female hormones that prevent ovulation (the release of an egg from an ovary). This medicine also causes ***changes in your cervical mucus and uterine lining, making it harder for sperm to reach the uterus and harder for a fertilized egg to attach to the uterus.***

(l) Norethisterone Enanthate + Estradiol Valerate

Guo-wei, S. (1994). Pharmacodynamic effects of once-a-month combined injectable contraceptives. *Contraception*, 371.

The combination has a ***suppressive effect on the endometrium.***

(m) Norethisterone + Ethinyl Estradiol + Ferrous Fumarate

Note: Norethindrone (also known as Norethisterone)
http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=6230

http://www.drugs.com/mtm/ethinyl-estradiol-and-norethindrone.html
http://www.drugs.com/pro/norethindrone-ethinyl-eestradiol-and-ferrous-fumarate.html

Ethinyl estradiol and norethindrone is a combination drug that contains female hormones that prevent ovulation (the release of an egg from an ovary). This medication also causes ***changes in your cervical mucus and uterine lining, making it harder for sperm to reach the uterus and harder for a fertilized egg to attach to the uterus.***

Combination oral contraceptives act by suppression of

gonadotropins. Although the primary mechanism of this action is inhibition of ovulation, other alterations include ***changes in the cervical mucus (which increase the difficulty of sperm entry into the uterus) and the endometrium (which reduce the likelihood of implantation).***

Ferrous fumarate is an iron supplement.

6.3 On The Abortifacient Nature Of Progestin-Only Hormonal Contraceptives. **---** Progestin-only hormonal contraceptives also affect the uterine lining. Goodman & Gilman's *The Pharmacological Basis of Therapeutics (12 ed.)*, a pharmacology textbook used worldwide, in its chapter entitled *"Contraception and Pharmacotherapy of Obstetrical and Gynecological Disorders",* states as follows:

> "**Progestin-Only Contraceptives.** Progestin-only minipills contain derivatives of 17□-alkyl-19-nortestosterone but do not contain an estrogen. Although they do inhibit ovulation to some degree, their efficacy also reflects changes in the cervical mucus that inhibit fertilization and ***endometrial changes that inhibit implantation.***"[22]

MedlinePlus, mentioned earlier as a public service of the U. S. National Library of Medicine and the National Institutes of Health, states that:

> "Progestin is a female hormone. It works by preventing the release of eggs from the ovaries (ovulation) and ***changing*** the cervical mucus and ***the lining of the uterus.***" http://www.nlm.nih.gov/medlineplus/druginfo/meds/a602008.html

Medline Plus also explicitly states the following about the effect of progestin-only contraceptives on the uterine lining:

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[22] Brunton. L.L., Chabner, B. A., & Knollmann, B. C. (Eds.). (2010), p. 1836. Mcgraw-Hill. Medical Publishing Division.

"The progesterone in birth control pills creates a thick cervical mucus, making it difficult for sperm to reach the uterus. ***It also impedes an egg from attaching itself to the uterine lining (endometrium) because of changes in the cellular structure of the lining."***
http://www.nlm.nih.gov/medlineplus/ency/presentations/100108_6.htm
Update Date: 2/26/2012

The **Progestin-Only** generic groups are:

(a) Medroxyprogesterone acetate
http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020246s036lbl.pdf

The US FDA website in the full prescribing information on the mechanism of action of Depo-provera, a brand of medroxyprogesterone acetate, states that this drug "inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and ***results in endometrial thinning.*** These actions produce its contraceptive effect."

(b) Lynestrenol
http://www.mims.com.ph/PHILIPPINES/drug/info/Daphne/?type=full

The MIMS Philippines website provides the following information on Lynestrenol, in its full information on "Daphne", a brand of hormonal contraceptives which has Lynestrenol as its active ingredient: "Daphne stops ovulation, ***thins the lining of the uterus*** and thickens the cervical mucus. In combination, these actions prevent pregnancy."

(c) Desogestrel
http://www.netdoctor.co.uk/sex-and-relationships/medicines/cerazette.html

The netdoctor.co.uk, a leading health website in the United Kingdom, provides the following information: "Desogestrel works as a contraceptive primarily by preventing

the release of an egg from the ovary (ovulation). It also acts by increasing the thickness of the natural mucus at the neck of the womb, making it more difficult for sperm to cross from the vagina into the womb. By preventing sperm entering the womb, successful fertilisation of any eggs that are released is less likely. ***Desogestrel also acts to change the quality of the womb lining (endometrium). This prevents the successful implantation of any fertilised eggs onto the wall of the womb, thereby preventing pregnancy."***

(d) Norethisterone
http://www.mims.com/PHILIPPINES/Home/GatewaySubscription/?generic=norethisterone

Norethisterone has typical effects of a progestogen and ***converts the endometrium from the proliferative to the secretory phase*** (which is a thin, devasculating lining, physiologically unreceptive to receiving and sustaining a human embryo).

(e) Lynestrenol
http://www.medicineindia.org/pharmacology-for-generic/2758/lynestrenol

As a synthetic oral progestogen, Lynestrenol has similar effects as that of the natural progesterone hormone. It has a ***strong progestational effect on the uterine endometrium by transforming the proliferative endometrium into a secretory one***.

6.4 On The Abortive Mechanism Of Action Of The Five Hormonal Contraceptives Included In The Philippine National Drug Formulary. --- Five (5) hormonal contraceptives are listed in the Philippine National Drug Formulary (PNDF), Vol. 1, 7th Edition 2008,[23] which according to the DOH Center for Pharmaceutical Assessment and Monitoring (CEPAM) is the one currently in use. These are: (1) ethynilestradiol + levonorgestrel; (2) ethinylestradiol +

[23]Pages 79-80 of the PNDF/Essential Drugs List; http://www.philhealth.gov.ph/partners/providers/pdf/PNDFvol1ed7_2008.pdf - accessed on September 29, 2013.

desogestrel; (3) ethynilestradiol + norgestrel; (4) ethinylestradiol + norethisterone; and (5) medroxyprogesterone. **As already shown earlier, all five hormonal contraceptives listed as such in the PNDF/EDL cause changes in the uterine lining, making it harder for the fertilized egg to implant.**

Executive Order No. 49, s. 1993 directed "the mandatory use of The Philippine National Drug Formulary (PNDF) Volume 1 as basis for procurement of drug products by the government."[24]

6.5 It Is Misplaced For The Respondents To Cite The World Health Organization (WHO) Because WHO Advocates And Promotes SAFE ABORTION. --- The Philippine Constitution stands out as a constitution that reverently protects the life of the unborn from conception. It is not proper to look at other models or jurisprudence for comparison as they may not accurately reflect the same reverence that we bestow upon the unborn. The citation by the respondents of the WHO certification, while the genuineness and due execution thereof are not necessarily admitted, is misplaced. It is a known fact that the World Health Organization (WHO) is for abortion. In fact, it just released an update of its 2003 publication - *Safe abortion: technical and policy guidance for health systems.* The substantial revisions in the 2012 update reflect developments not only in safe abortion methods and clinical care, but also in the application of human rights principles in policy-making and in legislation related to induced abortion. The updated publication contained recommendations that provide guidance about the range of safe options available to women seeking an elective abortion and highlight the importance of having the woman participate in the choice of abortion method, pain control and post-abortion contraception.[25] Need we say more?

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[24] http://uhmis2.doh.gov.ph/doh_ncpam/images/publication/pndf.pdf - accessed on September 29, 2013.

[25] *Bulletin of the World Health Organization* 2012;90:712-712. doi: 10.2471/BLT.12.107144 http://www.who.int/bulletin/volumes/90/9/12-107144/en/#.UZ10kjlO5u0.email; accessed on May 20, 2013.

6.6 Summary of Information on Abortifacient and Harmful Effects with Reference to Corresponding Sources. **--- Please see TABLE (Volume 1).**

6.7 --- CONCLUSION. After a diligent, careful, thorough and judicious reading and examination of all the reference materials, we have confidently arrived at the conclusion that: **Every single hormonal contraceptive, IUD and injectable, whether of a "combined estrogen-progesterone formulation" or of a "progestin-only formulation", by its mechanism of action, causes changes in the uterine lining which make it harder for a fertilized egg to attach to the uterus, i.e., inhibit implantation. Such changes "induce the prevention of the fertilized ovum to reach and be implanted in the mother's womb", as stated in the definition of "abortifacient" in R. A. 10354. This then may induce "abortion or the destruction of a fetus insde the mother's womb". All hormonal contraceptives, IUDs and injectables by causing such changes, can cause the death of newly-conceived life in the womb. Therefore, all hormonal contraceptives, IUDs and injectables sold in the Philippine market and approved by and registered by the FDA are Abortifacients. Further, they also are harmful to the health of women.**

7. Adverse Effects of Hormonal Contraceptives, IUDs and Injectables.

Let us consider the following glaring and disturbing findings. Shown below are the summaries of some studies made and their respective findings and results. The complete texts of the articles taken from various scientific journals accessed through the electronic resources collections of the UST Miguel de Benavides Library and the Makati Medical Center Library, as well as from various websites online are compiled and attached in Volume 2: --

I. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies

Collaborative Group on Hormonal Factors in Breast Cancer

SOURCE: *Lancet* 1996; 1713-27

Individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 studies conducted in 25 countries were collected, checked, and analysed centrally.

The studies included in this collaboration represent about 90% of the epidemiological information on the topic, and what is known about the other studies suggests that their omission has not materially affected the main conclusions.

*Overall, there is a **slight increased relative risk of breast cancer** in women who had ever used oral contraceptives compared with women who had never used them, and the excess was **statistically significant** (relative risk 1.07 [SD 0.02], 2p=0.00005).*

Results:

The results provide strong evidence that:

1. While women are **taking combined oral contraceptives** and **in the 10 years after stopping** there is a **small increase in the relative risk of having breast cancer diagnosed (relative risk [95% Cl]**

    - **current users** 1.24 [1.15-1.33], 2p<0.00001;
    - **1-4 years after stopping** 1.16 [1.08-1.23], 2p=0.00001;

- **5-9 years after stopping** 1.07 [1.02-1.13], 2p=0.009).

Other findings:

1. Regarding age at first use, the **relative risk** was slightly greater than 1.0 for each of the five age groups and was **largest for women who started use as teenagers**.

    - For recent users the relative risks were greater for those who began before age 20 than for those who began at later ages and tended to decline with increasing age at diagnosis.

2. There was **no significant variation in the relative risks associated with use of specific types of estrogen or of progestogen**, either in recent or in past users.

3. There were **no significant trends with duration of use among women who had used low-dose, medium-dose, or high-dose preparations**.

4. **Hormonal contraceptives containing progestagens only.** The amount of information available was limited, but the results were broadly similar to those found for combined oral contraceptives:

    - some evidence of an **increase in risk for use in the previous 5 years** (relative risk 1.17 [SD 0.09], p=0.06, for oral preparations; 1.17 [SD=0.13], NS, for injectable progestagens)
    - **no evidence of an increase in risk 10 or more years after stopping use** (0.99 [SD=0,13], NS, for oral preparations; 0-94 [SD=0-13], NS, for injectable preparations)
    - no apparent residual effects of duration of use or age at first use, but the numbers are too small to exclude such effects with any certainty

II. Oral Contraceptive Use as a Risk Factor for Premenopausal Breast Cancer: A Meta-analysis

Chris Kahlenborn, MD; Francesmary Modugno, PhD, MPH; Douglas M. Potter, PhD; Walter B. Severs, PhD

SOURCE: *Mayo Clinic Proceedings;* Oct 2006; 81(10), 1290-1302

This is a meta-analysis of 39 case-control studies conducted in or after 1980 to clarify the possible association between oral contraceptive use and breast cancer risk in premenopausal women or women younger than 50 years.

More recent studies have noted an increase in risk among oral contraceptive users, **especially among women who took them before a first full-term pregnancy** (FFTP). Women who are exposed to carcinogens before FFTP may have a higher risk of developing breast cancer because the glandular tissue of the breast has not yet undergone the further differentiation associated with pregnancy. This differentiation inhibits carcinogenic initiation and may explain the natural protection that pregnancy has been shown to confer.

Results:

Consistent with the recent International Agency for Research on Cancer (IARC) classification of oral contraceptives as group 1 carcinogens. This meta-analysis suggests that oral contraceptives are associated with an increase in premenopausal breast cancer risk, especially among women who use oral contraceptives before FFTP.

Overall, oral contraceptive use is associated with an **increased risk of breast cancer** among premenopausal women or women younger than 50 years, with a pooled OR of 1.19 (1.09-1.29). The greatest risk appears to be for parous women who use oral contraceptives before the first full-term pregnancy (FFTP).

1. The risk for breast cancer with oral contraceptive use before FFTP (OR 1.44, 95% CI 1.28 to 1.62) was **higher** than if oral contraceptives were used after FFTP (OR 1.15, 95% CI 1.06 to 1.26).

2. The association between oral contraceptive use and breast cancer risk **was highest for parous women** *(women who have given birth)* **who used oral contraceptives 4 or more years before FFTP** (OR 1.52, 95% CI 1.26-2.82).

3. Among parous women who **ever used** oral contraceptives, there is also an **increased breast cancer risk** (OR 1.29, 1.20 to 1.40).

4. Among nulliparous women *(women who have never given birth)*, there is **no significant difference** between those who **ever used** oral contraceptives (1.24, 95% CI 0.92-1.67) and those who **used oral contraceptives for 4 years or more** (1.29, 95% CI 0.85-1.96).

III. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies

International Collaboration of Epidemiological Studies of Cervical Cancer

SOURCE: *Lancet* 2007; 370:1609-21

Individual data on 16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 studies conducted in 26 countries were re-analysed centrally. About half of the studies were from less developed countries.

The data presented here represent about 85% of the known published worldwide epidemiological evidence on risk of invasive cervical cancer and of CIN3/carcinoma in situ, and the use of combined oral contraceptives. Results from studies for which data were not included are generally consistent with the main findings.

Results:

Overall, the relative risk of cervical cancer is increased in current users of oral contraceptives and declines after use ceases.

Current and recent use of combined oral contraceptives is associated with an increase in the risk of invasive cervical cancer. The risk increased significantly with increasing duration of use and was highest in current users (p<0.0001).

Ten years' use of oral contraceptives from around age 20 to 30 years is estimated to **increase the cumulative incidence of invasive cervical cancer by age 50 from 7.3 to 8.3 per 1,000 in less developed countries** and from 3.8 to 4.5 per 1,000 in more developed countries.

1. The relative risk in current users increases with **increasing duration of oral contraceptive use** (p<0.0001), and was highest in current users.

    a. **Less than 5 years of use** 0.97 [0.90-1.04]; *no significant increase*
    b. **More than 5 years of use** 1.90 [1.69-2.13]; ***about a doubling of risk***

2. The relative risk declines with increasing time since last use (p<0.0001).

    a. By 10 or more years after last use, the risk is not significantly different from that in never users.

Other findings:

1. Age at first use and time since first use did not contribute as independent risk factors.

2. **Hormonal contraceptives containing progestagens only:**

    a. There is an **increase in risk for invasive cervical cancer associated with the use of progestagen-**

only injectable contraceptives for 5 years or more (relative risk 1.22 [1.01-1.46], p=0.03)

b. **There is no clear effect of time since last use.**

IV. Cervical cancer and use of hormonal contraceptives: a systematic review

Jennifer S Smith, Jane Green, Amy Berrington de Gonzalez, Paul Appleby, Julian Peto, Martyn Plummer, Silvia Franceschi, Valerie Beral

SOURCE: *Lancet* 2003; 361:1159–67

A total of 12,531 women with invasive or in situ cervical cancer from 28 studies were eligible for this systematic review.

Overall, the relative risk of cervical cancer increases with increasing duration of oral contraceptive use.

Results:

1. The relative risk of cervical cancer increased with increasing duration of use:

   - **less than 5 years** 1.1 (95% CI 1.1-1.2)
   - **5–9 years** 1.6 (1.4-1.7),
   - **10 years or longer** 2.2 (1.9-2.4)

2. The relative risk declines with increasing time since last use. Among women who used oral contraceptives for 5 years or longer:

   - **Current use or use that ceased less than 8 years ago** 2.1 (1.8-2.4)
   - **Use that ceased more than 8 years ago** 1.4 (1.1-1.9)

3. Use of injectable contraceptives for 5 years or longer was associated with a slight increase of borderline

significance in the relative risk of cervical cancer: relative risk 1.2 (1.0-1.6)

V. Effect of oral contraceptives on risk of cervical cancer in women with human papillomavirus infection: the IARC multicentric case-control study

Victor Moreno, F Xavier Bosch, Nubia Muñoz, Chris J L M Meijer, Keerti V Shah, Jan M M Walboomers, Rolando Herrero, Silvia Franceschi, for the International Agency for Research on Cancer (IARC) Multicentric Cervical Cancer Study Group

SOURCE: *Lancet* 2002; 359: 1085–192

The aim of this study was to assess how use of oral contraceptives affected risk of cervical cancer in women who tested positive for HPV DNA.

Data were pooled from eight case-control studies of patients with histologically confirmed invasive cervical carcinoma (ICC) and from two studies of patients with carcinoma in situ (ISC). 1,676 patients with squamous cell carcinoma and 255 controls were positive for HPV DNA, and were thus included in this analysis.

Long-term use (5 years or longer) of oral contraceptives could be a cofactor that ***increases risk of cervical carcinoma by up to three-fold in women who are positive for cervical HPV DNA****. In the absence of worldwide information about HPV status, extra effort should be made to include long-term users of oral contraceptives in cervical screening programmes.*

Results:

1. Risk was increased for **5 or more years of** use:
    - The odds ratio for use of oral contraceptives was 2.82 (95% CI 1.46–5.42) for **5–9 years**.
    - The odds ratio for use of oral contraceptives was 4.03 (2.09–8.02) for use for **10 years or longer**.

2. These risks did not vary by time since first or last use.

VI. Mortality associated with oral contraceptive use: 25 year follow up of cohort of 46 000 women from Royal College of General Practitioners' oral contraception study

Valerie Beral, Carol Hermon, Clifford Kay, Philip Hannaford, Sarah Darby, Gillian Reeves

SOURCE: *British Medical Journal* 1999;318:96–100

This is a cohort study with a 25-year follow up, to describe the long term effects of the use of oral contraceptives on morbidity and mortality.

1,400 general practitioners recruited 46,000 women, half of whom were using oral contraceptives at recruitment in 1968-1969. Median age at end of follow up was 49 years. 75% of the original cohort was “flagged” on the NHS central registers.

Main outcome measures relative risks of death were adjusted for age, parity, social class, and smoking.

Results:

Among current and recent (within 10 years) users:

1. There was **an increased risk of death from cervical cancer**: relative risk of death from cervical cancer 2.5 (1.1 to 6.1; P = 0.04), and

2. There was an **increased risk of death from cerebrovascular disease**: relative risk of death from cerebrovascular disease 1.9 (1.2 to 3.1, P = 0.009).

By contrast, for women who had stopped use >10 years previously there were no significant excesses or deficits either

overall or for any specific cause of death.

Conclusion:

Oral contraceptives seem to have their main effect on mortality while they are being used and in the 10 years after use ceases. Ten or more years after use ceases mortality in past users is similar to that in never users.

VII. Risk of Acute Thromboembolic Events With Oral Contraceptive Use: A Systematic Review and Meta-analysis

Rachel Peragallo Urrutia, MD, MSCR, Remy R. Coeytaux, MD, PhD, Amanda J. McBroom, PhD, Jennifer M. Gierisch, PhD, MPH, Laura J. Havrilesky, MD, MHSc, Patricia G. Moorman, PhD, William J. Lowery, MD, Michaela Dinan, PhD, Vic Hasselblad, PhD, Gillian D. Sanders, PhD, and Evan R. Myers, MD, MPH

SOURCE: *Obstetrics and Gynecology* 2013;122:380–389

Since the 1960s, several life-threatening vascular events have been associated with oral contraceptive pills (OCP) use. These include venous thromboembolic disease (encompassing deep vein thrombosis [DVT] and pulmonary embolism [PE]), stroke (both thrombotic and hemorrhagic), and myocardial infarction (MI). Given the large number of women currently using OCPs, an increased risk of thromboembolic events associated with OCP use is an important public health issue.

This is a meta-analysis of fifty (50) controlled studies (cohort or case–control study) or pooled patient-level meta-analysis studies published from 1995 to 2012.

Objective: To estimate the risk of venous thromboembolism, stroke, or myocardial infarction (MI) associated with the use of OCPs and to describe how these risks vary by dose or formulation.

Results:

Current use of combined OCPs is associated with a **threefold increased risk of venous thromboembolism**, a **twofold increased risk of ischemic stroke**, and an indeterminate effect on risk of MI associated with OCP use.

1. There is an **increased risk of <u>venous thromboembolism</u> associated with current compared with noncurrent OCP use.**

    a. The estimated odds ratio (OR) of venous thromboembolism in current compared with noncurrent OCP users was 2.97 (95% CI 2.46–3.59).

    b. There was no difference in the incidence of venous thromboembolism by estrogen dose level or by progestin generation.

2. There is an **increased risk of <u>ischemic stroke</u> associated with current compared with noncurrent OCP use.**

    a. The estimated OR for ischemic stroke among current compared with noncurrent OCP users of 1.90 (95% CI 1.24–2.91).

    b. **Incidence of ischemic and undifferentiated stroke was significantly increased among users of high compared with low estrogen dose** (OR 2.37, 95% CI 1.05–5.38).

3. There is **high strength of evidence for increased risk of MI associated with first-generation OCP use.** The estimates of ORs for the incidence of MI for current compared with noncurrent OCP users is 3.37 (95% CI 2.04–5.54) for first-generation progestin OCP users, 1.79 (95% CI 1.16–2.75) for second-generation progestin users, and 1.34 (95% CI 0.91–1.98) for third-generation users.

VIII. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a

population-based cohort study

Naomi Gronich MD, Idit Lavi MSc, Gad Rennert MD PhD

SOURCE: *Canadian Medical Association Journal* 2011;183:1319–1325

This is a population-based historical cohort study of 329,995 women in Israel for whom at least one combined oral contraceptive prescription had been dispensed between Jan. 1, 2002, and Dec. 31, 2008, and who were between 12 and 50 years of age throughout the study period.

329,995 women 12–50 years of age were included. The authors followed the cohort until 2009, and identified first-time diagnoses of thrombotic events, specifically deep vein thrombosis, pulmonary embolism, transient ischemic attack and cerebrovascular accident.

Results:

Use of drospirenone-containing combined oral contraceptives was associated with a significantly increased risk of venous thrombotic events (deep vein thrombosis and pulmonary embolism) but not arterial thrombotic events (transient ischemic attack and cerebrovascular accident), relative to use of second- or third-generation combined oral contraceptives.

1. The **risk of venous thrombotic events was significantly greater** among drospirenone users than among users of third-generation combined oral contraceptives (RR 1.43, 95% CI 1.15–1.78).

2. Drospirenone was also associated with **increased risk of venous thrombotic events** relative to second-generation combined oral contraceptives (RR 1.65, 1.02–2.65).

3. The difference in risk between second- and third-generation combined oral contraceptives was not statistically significant (RR 1.38, 95% CI 0.90–2.11).

There are other studies that already state an increased risk for venous thrombotic complications among third-generation combined oral contraceptives compared with non-users.

Hence, it can be surmised that **drosperinone has an <u>even greater</u> increased risk for venous thrombotic complications compared with non-users.**

IX. Third generation oral contraceptives and risk of venous thrombosis: meta-analysis

Jeanet M Kemmeren, Ale Algra, Diederick E Grobbee

SOURCE: *British Medical Journal* 2001;323:1–9

This is a meta-analysis of cohort and case-control studies published from October 1995 to December 2000, assessing risk of venous thromboembolism among women using oral contraceptives before October 1995.

Results:

Third generation oral contraceptives are associated with a **1.7-fold increased risk of venous thrombosis** compared with second generation oral contraceptives. Similar risks were found when oral contraceptives containing desogestrel or gestodene were compared with those containing levonorgestrel.

1. The odds ratio for third versus second generation preparations among first time users was 3.1 (2.0 to 4.6).

2. The odds ratio was 2.5 (1.6 to 4.1) for short term users, and 2.0 (1.4 to 2.7) for longer term users.

X. Laparoscopic removal of an intra-abdominal intrauterine device: case and systematic review

Richdeep S. Gill, Dereck Mok, Matthew Hudson, Xinzhe Shi, Daniel W. Birch, Shahzeer Karmali

SOURCE: *Contraception* 2012;85:15-18

Uterine perforation secondary to an intrauterine device (IUD) is a rare but serious complication. It is estimated that the rate of perforation is between 0 and 1.3 per 1000 patients.

The World Health Organization recommends that all displaced IUDs be removed promptly. Perforation of the uterus necessitates surgical removal of IUDs due to the potential for bowel perforation or obstruction.

In the past, the presence of adhesions and perforation of viscera often resulted in the need for a laparotomy to successfully remove the IUD; however, advances in laparoscopic technique have allowed surgeons to safely retrieve perforated IUDs.

Objective: To analyze uterine perforation by an IUD and assess laparoscopic vs. open methods for removal of a perforated IUD.

Results:

This study reviewed human case series and case reports of female adults (>18 years old) with a uterine perforation secondary to an IUD written between 1970 and 2009.

49 articles met the inclusion criteria following careful screening. These included 15 case series and 34 case studies, which identified a total of 179 cases of perforated IUDs in which laparoscopic removal was attempted.

1. The mean age of the patients was 26 years old, ranging from 17 to 49 years old.

2. Diagnostic laparoscopy was successfully performed in all 179 patients.

a. The perforated IUDs were found in a variety of locations including the omentum (26.7%), pouch of Douglas (21.5%), colonic lumen secondary to perforation (10.4%), myometrium (7.4%), broad ligament (6.7%), free within the abdomen (5.2%), small bowel serosa (4.4%), colonic serosa (3.7%) and mesentery (3%).

b. Rare locations such as the bladder, appendix, abdominal wall, fallopian tube, ovary, retroperitoneum and small bowel with perforation were also reported.

3. Subsequently, the removal of the perforated IUD was completed laparoscopically in 64.2% (115/179) of cases.

4. Laparotomy either after diagnostic laparoscopy or conversion after attempted laparoscopic removal was performed in 34.6% (62/179) of cases.

5. Two cases utilized a combination of laparoscopic and endoscopic techniques to remove the perforated IUDs. This involved performing a colonoscopy or hysteroscopy to aid laparoscopic removal of the IUD.

6. In the 19 cases of small bowel or colonic perforation secondary to the IUD, laparoscopic removal and subsequent repair/resection of the bowel was performed in only 21% (4/19) of cases. **More cases (68% or 13/19) required immediate or subsequent conversion to laparotomy and open resection/repair of the viscera.**

XI. Pregnancy outcome in women with an intrauterine contraceptive device

Hadas Ganer, BA; Amalia Levy, PhD; Iris Ohel, MD; Eyal Sheiner, MD, PhD

SOURCE: *American Journal of Obstetrics and Gynecology* 2009;201:381.e1-5

This is a population-based study comparing pregnancies

of at least 22 weeks of gestation among women

(1) with an IUD,

(2) after IUD removal at the beginning of the pregnancy,

(3) without IUD

delivered during the years 1988-2007 at the Soroka University Medical Center.

Objective: To compare labor characteristics and perinatal outcomes among women with an IUD, after IUD removal at the beginning of the pregnancy, and without IUD.

Results:

During the 19-year period of the study, 292 singleton pregnancies were of women who conceived with an IUD, which was removed in 194 women during early pregnancy. All IUDs were copper-based devices.

The major finding of this population-based study was that conceiving with an IUD is a significant risk factor for adverse maternal and perinatal outcomes. Moreover, a significant linear-by-linear association exists between (1) a retained IUD throughout pregnancy, (2) an IUD that was removed during early pregnancy, and (3) no IUD, **and adverse outcomes – including PROM, placental abruption, placenta previa, preterm delivery, cesarean delivery, Apgar score lower than 7 at 5 minutes, low birthweight, congenital malformations, and chorioamnionitis.**

1. **Both IUD usage and removal were found to be independent risk factors for preterm delivery (< 37 weeks).**

2. **Both IUD usage and removal were found to be independent risk factors for chorioamnionitis.**

The removal of the device in early pregnancy reduces

the risk for chorioamnionitis and preterm delivery, but does not fully diminish it in comparison to pregnancies with no such exposure.

XII. Different combined oral contraceptives and the risk of venous thrombosis: systematic review and network meta-analysis

Bernardine H Stegeman, Marcos de Bastos, Frits R Rosendaal, A van Hylckama Vlieg, Frans M Helmerhorst, Theo Stijnen, Olaf M Dekkers

SOURCE: *British Medical Journal* 2013;347:f5298

This is a systematic review and network meta-analysis of studies published up to 22 April 2013.

Objective: To provide a comprehensive overview of the risk of venous thrombosis in women using different combined oral contraceptives.

Results:

26 studies reported in 25 articles were included (one article presented two studies).

All combined oral contraceptives investigated in this analysis were associated with an **increased risk of venous thrombosis**. The effect size depended both on the progestogen used and the dose of ethinylestradiol.

Overall, combined oral contraceptive use increased the risk of venous thrombosis fourfold.

1. Compared with non-users, the risk of venous thrombosis in users of oral contraceptives with a first generation progestogen increased 3.2-fold (95% confidence interval 2.0 to 5.1), 2.8-fold (2.0 to 4.1) for second generation progestogens, and 3.8-fold (2.7 to 5.4) for third generation progestogens.

2. The risk of venous thrombosis in second generation progestogen users was similar to the risk in first generation users (relative risk 0.9, 0.6 to 1.4).

3. Third generation users had a slightly higher risk than second generation users (1.3, 1.0 to 1.8).

4. Restricted to studies with an identical classification of generations (see methods section for classification used), the results of each generation compared with non-use remained the same (first generation relative risk 3.2, 95% confidence interval 1.6 to 6.4; second generation 2.6, 1.5 to 4.7; third generation 3.5, 2.0 to 6.1).

XIII. Thrombotic Stroke and Myocardial Infarction with Hormonal Contraception

Øjvind Lidegaard, Dr. Med. Sci., Ellen Løkkegaard, Ph.D., Aksel Jensen, M.Sc., Charlotte Wessel Skovlund, M.Sc., and Niels Keiding, M.Sc.

SOURCE: *The New England Journal of Medicine* 2012; 366:2257-66

This is an open historical cohort study of Danish women, 15 to 49 years old, for a 15-year period, from January 1995 through December 2009.

Objective: To assess the risks of thrombotic stroke and myocardial infarction associated with the use of various types of hormonal contraception, according to estrogen dose, progestin type, and route of administration.

Results:

The study cohort included 1,626,158 women, with 14,251,063 person-years of observation. 3311 thrombotic strokes (21.4 per 100,000 person-years) and 1725 myocardial infarctions (10.1 per 100,000 person-years) occurred.

Although the absolute risks of thrombotic stroke and myocardial infarction associated with the use of hormonal contraception were low, the risk was increased by a factor of **0.9 to 1.7** with oral contraceptives that included ethinyl estradiol at a dose of **20 □g** and by a factor of **1.3 to 2.3** with those that included ethinyl estradiol at a dose of **30 to 40 □g**, with relatively small differences in risk according to progestin type.

1. As compared with nonuse, **current use** of oral contraceptives that included **ethinyl estradiol** at a dose of **30 to 40 □g** was associated with an **increased risk for thrombotic stroke and myocardial infarction, according to progestin type:**

    a. Norethindrone: relative risk for thrombotic stroke 2.2 (95% CI 1.5 to 3.2) and myocardial infarction 2.3 (1.3 to 3.9)
    b. Levonorgestrel: 1.7 (1.4 to 2.0) and 2.0 (1.6 to 2.5)
    c. Norgestimate: 1.5 (1.2 to 1.9) and 1.3 (0.9 to 1.9)
    d. Desogestrel: 2.2 (1.8 to 2.7) and 2.1 (1.5 to 2.8)
    e. Gestodene: 1.8 (1.6 to 2.0) and 1.9 (1.6 to 2.3)
    f. Drospirenone: 1.6 (1.2 to 2.2) and 1.7 (1.0 to 2.6)

2. With **ethinyl estradiol** at a dose of **20 □g**, the corresponding relative risks according to progestin type were as follows:

    a. Desogestrel: 1.5 (1.3 to 1.9) and 1.6 (1.1 to 2.1)
    b. Gestodene: 1.7 (1.4 to 2.1) and 1.2 (0.8 to 1.9)
    c. Drospirenone: 0.9 (0.2 to 3.5) and 0.0.

3. Only small differences in risk were observed between women who took combination pills containing intermediate dose ethinyl estradiol (30 to 40 □g) and those who took low-dose ethinyl estradiol (20 □g).

    Thrombotic stroke (P = 0.24 for trend)

    a. 20 □g: 1.60 (95% CI, 1.37 to 1.86)
    b. 30 to 40 □g: 1.75 (95% CI, 1.61 to 1.92)
    c. 50 □g: 1.97 (95% CI, 1.45 to 2.66)

    Myocardial infarction (P<0.001 for trend)

a. 20 □g: 1.40 (95% CI, 1.07 to 1.81)
b. 30 to 40 □g: 1.88 (95% CI, 1.66 to 2.13)
c. 50 □g: 3.73 (95% CI, 2.78 to 5.00)

XIV. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9

Øjvind Lidegaard, Lars Hougaard Nielsen, Charlotte Wessel Skovlund, Finn Egil Skjeldestad, Ellen Løkkegaard

SOURCE: *British Medical Journal* 2011;343:d6423

This is a national historical registry based cohort study among non-pregnant Danish women aged 15-49 with no history of thrombotic disease and followed from January 2001 to December 2009.

Objective: To assess the risk of venous thromboembolism from the use of combined oral contraceptives according to progestogen type and oestrogen dose.

Results:

Within 8,010,290 women years of observation, 4307 first ever venous thromboembolic events were recorded and 4246 included, among which 2847 (67%) events were confirmed as certain.

1. Compared with non-users of hormonal contraception, **current users** of oral contraceptives with **levonorgestrel** were at a **three-fold increased risk** for confirmed venous thrombosis and **users** of oral contraceptives with **desogestrel, gestodene, drospirenone, or cyproterone acetate** a **six- to seven-fold increased risk**.

    a. Levonorgestrel: relative risk 2.9 (95% confidence interval 2.2 to 3.8)
    b. Gestodene: 6.2 (5.6 to 7.0)
    c. Desogestrel: 6.6 (5.6 to 7.8)

d. Drospirenone: 6.4 (5.4 to 7.5)

2. Users of oral contraceptives with desogestrel, gestodene, or drosperinone were at **twice the risk of venous thromboembolism** compared with users of oral contraceptives with levonorgestrel.

   a. Gestodene: rate ratio 2.1 (95% CI 1.6 to 2.8)
   b. Desogestrel: 2.2 (1.7 to 3.0)
   c. Drospirenone: 2.1 (1.6 to 2.8)

3. The relative risk of venous thromboembolism from using oral contraceptives with norethisterone, levonorgestrel, desogestrel, or gestodene **decreased with decreasing oestrogen dose**, whereas no difference was apparent between oral contraceptives with drospirenone and either 30 □g ethinylestradiol or 20 □g ethinylestradiol.

   Combined with 30 □g ethinylestradiol

   a. Levonorgestrel: relative risk 2.19 (95% confidence interval 1.74 to 2.75)
   b. Gestodene: 4.23 (3.87 to 4.63)
   c. Desogestrel: 4.21 (3.63 to 4.87)
   d. Drospirenone: 4.47 (3.91 to 5.11)

   Combined with 20 □g ethinylestradiol

   a. Gestodene: 3.50 (3.09 to 3.97)
   b. Desogestrel: 3.26 (2.88 to 3.69)
   c. Drospirenone: 4.84 (3.19 to 7.33)

XV. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel: nested case-control study based on UK General Practice Research Database

Lianne Parkin, Katrina Sharples, Rohini K Hernandez, Susan S Jick

SOURCE: *British Medical Journal* 2011;342:d2139

This is a case-control study nested in a cohort of users of oral contraceptives containing 30 □g oestrogen in combination with either drospirenone or levonorgestrel between 1 May 2002 and 30 September 2009.

Objective: To examine the risk of non-fatal idiopathic venous thromboembolism in current users of a combined oral contraceptive containing drospirenone, relative to current users of preparations containing levonorgestrel.

Results:

61 cases and 215 controls were included in the study. Among the 61 cases, 27 had a diagnosis of deep vein thrombosis and 34 had pulmonary embolism.

Women who were current users of the oral contraceptive containing **drospirenone** were about **three times as likely to develop idiopathic venous thromboembolism** as were current users of contraceptives containing levonorgestrel.

1. The matched odds ratio (adjusted for body mass index) in the case-control analysis was 3.3 (95% confidence interval 1.4 to 7.6).

2. The age adjusted incidence rate ratio in the cohort analysis was 2.7 (95% confidence interval 1.5 to 4.7).

XVI. The venous thrombotic risk of oral contraceptives, effects of oestrogen dose and progestogen type: results of the MEGA case-control study

A van Hylckama Vlieg, F M Helmerhorst, J P Vandenbroucke, C J M Doggen, F R Rosendaal

SOURCE: *British Medical Journal* 2009;339:b2921

This is a population based case-control study among pre-menopausal women aged 18-50 years with a first episode of

deep venous thrombosis (leg or arm) or pulmonary embolism between March 1999 and September 2004.

Objective: To assess the thrombotic risk associated with current oral contraceptive use with a focus on dose of oestrogen and type of progestogen.

Results:

1524 female patients and 1760 controls were included.

Overall, **current oral contraceptive use was associated with a fivefold increased risk of venous thrombosis** (odds ratio 5.0, 95% CI 4.2 to 5.8). Risk clearly differed by type of progestogen and dose of oestrogen.

1. Compared with non-use, **use of oral contraceptives was associated with increased risk of venous thrombosis.**

    a. Levonorgestrel: **almost fourfold increase** (odds ratio 3.6, 95% CI 2.9 to 4.6),
    b. Gestodene: 5.6-fold (95% CI 3.7 to 8.4) for those containing
    c. Desogestrel: 7.3-fold (5.3 to 10.0)
    d. Cyproterone acetate: 6.8-fold (4.7 to 10.0)
    e. Drospirenone: 6.3-fold (2.9 to 13.7)

2. **Third generation users had a higher risk than second generation users.** When different types of oral contraceptives were directly compared with those containing levonorgestrel (2nd generation), there was an **increased risk of thrombosis** associated with 3rd generation oral contraceptives and those containing cyproterone acetate and drosperinone.

    a. Gestodene: odds ratio 1.6, 95% CI 1.0 to 2.4
    b. Desogestrel: 2.0, 1.4 to 2.8
    c. Cyproterone acetate: 2.0, 1.3 to 3.0
    d. Drospirenone: 1.7, 0.7 to 3.9

3. With an oestrogen dose of 30 □g as the reference category, the thrombotic risk was similar with an oestrogen dose of 20 □g and **increased with an oestrogen dose of 50 □g**.

a. Oestrogen dose of 20 □g: 0.8 (95% CI 0.5 to 1.2)
b. Oestrogen dose of 50 □g: 1.9 (1.1 to 3.4)

4. The **risk of venous thrombosis was clearly highest during the first three months of use** (odds ratio 12.6, 95% CI 7.1 to 22.4). After one year, the risk of venous thrombosis for oral contraceptive users compared with non-users decreased to the overall estimate of a fivefold increased risk.

XVII. Oral contraceptive use and bone mineral density in premenopausal women: cross-sectional, population-based data from the Canadian Multicentre Osteoporosis Study

Jerilynn C. Prior, Susan A. Kirkland, Lawrence Joseph, Nancy Kreiger, Timothy M. Murray, David A. Hanley, Jonathan D. Adachi, Yvette M. Vigna, Claudie Berger, Lucie Blondeau, Stuart A. Jackson, Alan Tenenhouse, for the CaMOS Research Group

SOURCE: *Canadian Medical Association Journal* 2001;165(8):1023-9

The Canadian Multicentre Osteoporosis Study (CaMOS) is both a cross-sectional survey and a longitudinal cohort study.

This present study used data from the baseline evaluation collected in 1995–1997, from all women enrolled in the CaMOS aged 25–45 years who had not undergone a bilateral ovariectomy.

Objective: To assess the relation between oral contraceptive use and bone mineral density (BMD) in a population-based, 9-centre, national sample of women aged 25–45 years.

Results:

A total of 524 women met the criteria for inclusion.

Oral contraceptive use was associated with lower BMD measurements in the lumbar vertebrae and trochanter, and numerically lower levels were consistent across all measurement sites. *The difference is large enough between groups to be clinically important.*

1. Mean BMD values (adjusted for age, BMI and height) were 0.02–0.04 g/cm^2 (that is, 2.3%–3.7%) lower in oral contraceptive users, and were significantly lower in the spine and trochanter.

2. The BMD of the spine in oral contraceptive users was 1.03 (SD 0.12) g/cm^2 versus 1.07 (SD 0.12) g/cm^2 (95% confidence interval [CI] of difference –0.07 to –0.001) in those who had never used oral contraceptives.

3. BMD was neither related to the duration of oral contraceptive use nor to gynecological age at first use. Current and past users had similar BMD values.

Clinical Implications:

1. The lower BMD values in oral contraceptive users could translate into **increased fracture risks of the order of 20%–30%.**

2. Furthermore, these observations provide an explanation for the higher fracture rates in 2 large epidemiological studies of premenopausal oral contraceptive users compared with those who had never used oral contraceptives.

XVIII. Carcinogenicity of combined oestrogen-progestagen contraceptives and menopausal treatment

Vincent Cogliano, Yann Grosse, Robert Baan, Kurt Straif, Béatrice Secretan, and Fatiha El Ghissassi

WHO International Agency for Research on Cancer

SOURCE: *Lancet Oncology* 2005 6; 552-53

After examining all the evidence, **the Working Group classified combined oral contraceptives as carcinogenic to humans (group 1). This conclusion was made on the basis of sufficient evidence of cervical cancer, breast cancer in present users and recent users, and liver cancer in populations with a low frequency of hepatitis-B infection.**

CONCLUSORY

In a civilized society such as ours, the norm is to do no harm and to preserve and protect life in all of its manifestations—actual, probable, and even potential. The destruction of a human being, in whatever stage of development, is an act of irretrievable finality. One life is not fungible with another, and the value of each human life transcends ordinary measurement. It was once said: "*Any man's death diminishes me, because I am involved in Mankind; And therefore never send to know for whom the bell tolls; it tolls for thee.*"[26]

Just as our Constitutional Fathers consciously and deliberately took the safest approach to ensure that human life is protected from the very moment it exists and that no human life is killed, intentionally or unintentionally, in the face of compelling evidence of serious threat or risk to human life posed by contraceptive products and supplies, we implore the Food and Drug Administration whose bounden duty it is to protect and safeguard and the health and life of the public to take the most reverential and safest approach likewise by resolving every doubt in favour of protection and preservation

[26] John Donne, an English poet and lawyer.

of every human life from the moment of conception.

In this connection, ALFI stands ready to pursue any legal remedy or recourse whether civilly, criminally or administratively, against any agency, officer or employee thereof who may be responsible or accountable for any injury, illness or loss of life resulting from or incidental to the use of contraceptive drugs and devices.

PRAYER

ALFI prays that the Food and Drug Administration:

1. DENY ALL APPLICATIONS FOR RE-EVALUATION/RE-CERTIFICATION OF CONTRACEPTIVE DRUGS AND DEVICES;

2. RECALL ALL CONTRACEPTIVE DRUGS AND DEVICES IN THE PHILIPPINE MARKET AND SUBJECT ALL OF THEM TO THE REQUIRED RE-EVALUATION/RE-CERTIFICATION PROCESS;

3. ENSURE THAT NO CONTRACEPTIVE DRUGS AND DEVICES ARE SOLD, DISTRIBUTED OR OTHERWISE MADE AVAILABLE UNLESS AND UNTIL A CREDIBLE, TRANSPARENT AND JUDICIOUS RE-EVALUATION/RE-CERTIFICATION PROCESS IS CONDUCTED BY FDA;

4. GRANT ALFI AN ADDITIONAL THIRTY (30) DAYS FROM OCTOBER 08, 2014 OR UNTIL NOVEMBER 07, 2014 WITHIN WHICH TO FILE A SUPPLEMENTAL AND/OR INDIVIDUAL OPPOSITION, IF DEEMED NECESSARY.

Taguig City for the City of Muntinlupa, October 08, 2014.

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VOLUME 1

TABLE

(Summary of Relevant Information About Combined Oral Contraceptives & Progestin-Only Contraceptives with Printed Copies of Reference Materials)

VOLUME 2

PRINTED COPIES OF REFERENCE MATERIALS

A. Accessed Through the:

1. **UST Miguel de Benavides Library (as certified by Kaori B. Fuchigami)**

2. **Makati Medical Center Medical Library (as certified by Ma. Ana Patricia H. Alvia, MD)**

3. **Various Indicated Websites & Personal Online Subscription**

**B. How the Pill Works
John Wilks B. Pharm
MPS MAACP
Consultant Pharmacist
5/10/2009**