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Embryocidal Potential of Modern Contraceptives

The mechanism of action of contraceptive drugs and devices form an essential part of informed consent for patients considering various methods of family planning. Currently the literature is confusing at best, in part due to non-uniform definitions of basic terms, as well as the misinterpretation of endpoints. AAPLOG members take different positions on the philosophical issue of contraception use per se, which will not be addressed in this document. The purpose of this document is to investigate and summarize the current evidence-based concerns regarding potential embryocidal mechanisms of action of modern contraceptive drugs and devices.

Background

There are three reasons for concern about embryos conceived during the use of a particular contraceptive drug or device:

1. All contraceptive drugs and devices "fail" at a certain rate. As noted in a recent paper, ***"Unintended pregnancies occur with all contraceptive methods, including IUDs. This provides incontrovertible evidence that fertilization and implantation can occur, albeit rarely, with modern methods of contraception."***[1]

2. Since pregnancies can and do occur during the use of all contraceptive drugs and devices, then we know by definition that fertilization, which marks the beginning of an embryonic human organism, can and does happen with all contraceptive drugs and devices since by definition an embryo must be created for pregnancy to occur. That means embryos are created at a certain rate with all contraceptive drugs or devices.

3. The contraceptive drug or device will create a certain environment for the embryos created during their use. This environment may adversely affect embryo survival prior to and up to the point of yielding a positive pregnancy test at the end of the cycle (the contraceptive efficacy end point).

The remainder of this article will try to summarize what is known in the published medical literature about the environment facing an embryo who has been created

AAPLOG Committee Opinion. This document was developed by 15 authors on the Research Committee. Committee Opinions summarize best practices that form an important part of pro-life practice.

during the use of various kinds of contraceptive drugs or devices.

Brief Review of Reproductive Physiology

The symphony of events surrounding ovum release, fertilization, and implantation is coordinated primarily by the effects of hypothalamic signals on pituitary hormone release. FSH and LH released by the pituitary direct the subsequent, precisely timed elaboration of ovarian hormones estrogen and progesterone at specifically coordinated points in the cycle. The amount and timing of estrogen and progesterone by the ovary affect the peristalsis of the fallopian tube and the transcription of specific proteins in the endometrium, resulting ideally in an endometrium which facilitates fertilization and tubal transport of the embryo into an endometrial cavity conducive to implantation. Interference at any of these levels can result in environmental conditions which make the tubal transport, implantation, and subsequent survival of embryos less likely.

The important events in the menstrual cycle (cycle days approximate) are:

Day 3-7: Recruitment of ovarian follicles under the stimulation of rising levels of FSH.

Day 8-12: Selection and maturation of the dominant follicle in preparation for ovulation. Selection and maturation are also primarily under the control of FSH.

Day 11-13: Final preparation and release of the oocyte from the Graafian follicle. This event is primarily under the control of LH.

Day 12-14: Fertilization and the formation of the one-celled embryo (zygote). The one-celled embryo exists at the moment of sperm-egg membrane fusion, since at that moment and afterward the cell formed by sperm-egg membrane fusion exhibits all the characteristics of a new organism.[2]

Day 14-18 ovarian events: LH released by the pituitary luteinizes the cells in the Graafian follicle. The number of follicular cells thus transformed into progesterone-producing luteal cells is directly proportional to the area under the curve of LH release. Three conditions may follow, depending on the amount of LH release:

A. **Normal LH release and subsequent normal mid-luteal progesterone production.**

LH release may be normal in amount and duration, resulting in a normally functioning corpus luteum and normal luteal phase progesterone. This condition is labelled “ovulation” in a majority of contraceptive research papers.

B. **Threshold ovulatory LH with minimal luteinization of the Graafian follicle.**

The amount of LH released may allow for the rupture of the Graafian follicle and release of the ovum, but may be insufficient to transform the Graafian follicle into a normally functioning corpus luteum, resulting in insufficient production of progesterone in the luteal phase. This condition is termed “dysfunctional ovulation” in some more recent contraceptive literature, but can also be termed “active follicle like

structure" in the majority of contraceptive research papers, obscuring the fact that ovum release and subsequent fertilization is possible.[3] This condition is also termed "luteal phase defect" in the IVF literature. All of these terms describe a situation where insufficient progesterone production by the corpus luteum, which is produced after ovulation, results in excess embryonic loss and a decreased pregnancy rate at the end of the cycle. ***This is the mechanism of greatest concern for embryo formation under conditions which impede embryo survival.***

C. **Subthreshold LH.**

The amount of LH released is insufficient to allow for the rupture of the Graafian follicle. Thus, no ovum is released, and no embryo formed. ***This mechanism of action does not result in excess embryo demise, as no embryo would be formed under this circumstance.***

The extent to which each of these conditions takes place during the use of hormonal contraceptives depends on many factors, including the dose and type of progestin, the compliance of the patient, BMI, and individual patient-specific metabolic factors.

Day 14-18 embryonic events: While the Graafian follicular cells are being transformed into luteal cells capable of progesterone production, the embryo is travelling through the fallopian tube, propelled by both peristalsis and ciliary beat frequency, both of which are progesterone dependent activities.

During the time of embryonic tubal transit, the cells of the endometrium are also being transformed in preparation for implantation within in the endometrial cavity. These progesterone mediated changes provide for an optimal window of implantation corresponding to the time when the embryo arrives into the endometrial cavity.[4,5] The normal endometrial lining will only allow the embryo to implant during days 20-24 of the mother's cycle,[6] which corresponds to the time when the embryo is normally swept into the endometrial cavity. The process of implanting is complex, and involves a biochemical "cross-talk" between the embryo and his or her mother. A large number of estrogen and progesterone mediated molecular mediators must be present for implantation to happen. And many of these mediators are dependent upon precisely timed estrogen and progesterone priming of the endometrium.[7]

Implantation and the subsequent placental formation also require continued progesterone in sufficient amounts.[8] Inadequate progesterone, or the removal of progesterone either surgically by removal of the corpus luteum, or chemically by interference at the cellular level with natural progesterone production, or by the introduction of progesterone receptor blockers which directly block ovarian progesterone production at the level of the corpus luteum,[9,10] renders the endometrium incapable of continuing embryo sustenance, resulting in embryonic death.

Inflammatory reactions in the endometrium, as induced by the presence of both copper[11] and levonorgestrel IUDs,[12,13] can also lead to failure of implantation. Similarly, direct

mechanical disruption of the endometrium by "menstrual extraction" or IUD use can also lead to failure of implantation or the termination of an already implanted embryo.

Clarification of Terminology

The confusion of terms used to describe early embryonic events, especially in the medical literature, lends to unclear thinking about the effects of drugs and devices on embryos. Some of these equivocal terms include:

1. **Conception**

   Prior to the 1960s, the term "conception" was used in legal, lay, and medical literature synonymously with the term "fertilization," i.e., sperm-egg fusion. However, in the 1960s, ACOG redefined "conception" to be "the completion of implantation."[14] Redefining "pregnancy" to begin at "conception" deftly rendered "pregnancy" to not exist until implantation was "complete."

   This redefinition continues to have enormous legal and rhetorical implications, resulting in a confusion about the status of the human embryo prior to implantation, and yielding the term "abortifacient" to be semantically meaningless when used to describe the mechanism of action of most contraceptive drugs and devices, with the exception of the IUD and the progesterone receptor blockers mifepristone (RU-486) and ulipristal (Ella), both used as emergency "contraceptives" (only ulipristal is currently FDA-approved for this indication in the United States).

2. **Abortifacient**

   A drug or device which ends a "pregnancy." Since by ACOG definition, a "pregnancy" does not exist until "completion of implantation," most (but not all) contraceptive drugs would escape this moniker, since prevention of implantation would not be considered technically an "abortifacient" action.

3. **Ovulation**

   The scientific definition of "ovulation" is the release of the mature oocyte from the Graafian follicle.[15] However, the term "ovulation" has no uniform definition in the contraceptive literature. Sometimes, "ovulation" is used to signify follicular rupture as seen by ultrasound. Sometimes, "ovulation" is defined as a certain threshold progesterone level (no agreement as to what progesterone level should be used to signify ovulation).

   But most frequently, the term "ovulation" is used to mean follicular rupture *in addition to* a subsequent minimum threshold mid-luteal phase progesterone level.[16] There is no uniform agreement on what that minimum progesterone level should be. This definition precludes acknowledgement that ova are released, and embryos formed, under conditions of inadequate luteal phase progesterone production.

Occasionally in the more modern contraceptive literature, the condition of follicular rupture combined with inadequate mid-luteal progesterone levels is termed "dysfunctional ovulation."[17]

Clinical Questions and Answers

Q How is ovulation determined using the Hoogland criteria?

The clear consensus in the medical literature is that hormonal contraceptives "disrupt/inhibit" the process of ovulation. For the casual reader, "disruption/inhibition" implies complete prevention of egg release. However, most contraceptive researchers use the terms "disruption of ovulation" and "inhibition of ovulation" to include situations where follicular rupture occurs, but fertilization of the oocyte would take place in less than optimum conditions, i.e., "dysfunctional ovulations." The current contraceptive literature is both chaotic and ambiguous regarding criteria for ovum release.[18]

The most commonly used criteria for "ovulation" in the contraceptive literature are, 1) Hoogland,[19] and 2) Landgren.[20] Since the Hoogland criteria are currently by far the more frequently used, they will be reviewed briefly here. The Landgren criteria are older and do not involve the use of sonographically detected follicular rupture. Landgren criteria were used predominantly for older research on IUD mechanisms of action.

1. Hoogland Criteria for "Ovulation"

In an attempt to standardize the description of ovarian activity which occurs during the use of hormonal contraceptives, as well as to *"deal with the controversy over the increased incidence of ovarian cysts during the use of a low-dose pill,"* Hoogland[21] proposed a combination of proxy measures, both sonographic and endocrinological, to describe various types of hormonal activity with an end point to be able to detect hormonal activity which would most likely lead to a positive pregnancy test at the end of a cycle, i.e., a contraceptive "failure." With this efficacy endpoint in mind, he labelled certain combinations of sonographic activity and hormone production as "Ovulation," "Luteinized Unruptured Follicle (LUF)," "Active Follicle-Like Structure (FLS)," "None-Active Follicle-Like Structure," and "No Activity." It is very important to remember that the Hoogland categorization was based on the endpoint of *the likelihood of embryo survival to produce a subsequent positive pregnancy test*, not on actual correlation with egg release. Thus, Hoogland "ovulation" rate should be understood as the rate of *normal* ovulatory function resulting in embryo survival, but cannot be used to determine or exclude ovum release in cycles with dysfunctional ovulation.

The generally applied criteria are as follows:

a. "Hoogland Ovulation" requires:
    1. Dominant follicle >13mm diameter
    2. Ultrasound documentation of a decrease in follicle size by 50% or more within 2-4 days. When this criteria is met, the event is titled "Follicular Rupture."
    3. Serum estradiol (E) level >0.1nmol/L in follicular phase
    4. Serum progesterone (P) level >5nmol/L in luteal phase.

b. "Hoogland Luteinized Unruptured Follicle (LUF)" requires:
    1. Dominant follicle >13mm diameter
    2. Ultrasound documentation of a decrease in follicle size by less than 50% or occurring not within 2-4 days or not occurring at all. This ultrasound criteria is named "No follicular rupture" even in follicular rupture actually did occur but followed by less than "50%" shrinkage of the Graafian follicle by ultrasound. [This is the criteria which distinguishes "Hoogland Ovulation" from "Hoogland LUF."]
    3. Serum estradiol (E) level >0.1nmol/L in follicular phase
    4. Serum progesterone (P) level >5nmol/L in luteal phase

c. "Hoogland Active Follicle-Like Structure (FLS)" requires:
    1. Dominant follicle >13mm diameter
    2. Follicles may rupture or persist.
    3. Serum estradiol (E) level >0.1nmol/L in follicular phase
    4. Serum progesterone (P) level >5nmol/L in luteal phase

d. "Hoogland Non-Active Follicle-Like Structure" requires:
    1. Dominant follicle >13mm diameter
    2. Follicles may rupture or persist.
    3. Serum estradiol (E) level >0.1nmol/L in follicular phase
    4. No comment on serum progesterone

All four of these Hoogland categories involve follicles > 13mm in diameter. The distinction between these Hoogland categories is dependent upon arbitrarily assigned cut-off points which have not empirically been documented to actually correlate with egg release.

Distinguishing Hoogland "ovulation" from other Hoogland scores requires measuring a "50% reduction" in follicle size. This requires precisely catching the peak size of the follicle by ultrasound and then following that follicle until the minimum follicular size is obtained. This is obviously not going to occur with the twice weekly ultrasounds used in many of the

studies. Thus, Hoogland categories *b-d* are distinguished from Hoogland *a* ("ovulation") by criteria dependent on the skill of the sonographer, the quality of the ultrasound equipment, and the timing of the ultrasounds in relationship to follicular rupture, not on the actual presence or absence of ovum release. Clearly the potential for sonographic false negatives is tremendous, and non-visualization of follicular rupture meeting Hoogland criteria for "ovulation" does not rule out release of an ovum from the Graafian follicle.[22] Empirical evidence contradicts the assumption that "not meeting Hoogland 'ovulation' criteria" is a reliable indicator for excluding ovum release and embryo formation. Pregnancies have occurred in patients who did not meet Hoogland ovulation criteria.[23,24,25,26]

Of particular concern for medical professionals and patients who care about embryonic human life are Hoogland categories *b-d*. Even in the face of documented follicular rupture, if the mid-luteal progesterone levels are low or absent, this ovarian event is not classified as "ovulation" since embryo formation under these circumstances is unlikely to result in a positive pregnancy test. In fact, it is these "dysfunctional ovulations" – follicular ruptures with subsequent low mid-luteal progesterone production – which are consistent with luteal phase defect, and which pose the greatest risk of embryo demise.

2. Potential for False Negative in Hoogland Ovulation Criteria: *"Dysfunctional Ovulation"*

Croxatto[27] defines dysfunctional ovulation as "follicular rupture not preceded by an LH peak, or preceded by a blunted LH peak (<21 IU/L), or not followed by elevation of serum P over 12nmol/L." This definition could correspond to any of the following Hoogland classifications: "Hoogland Ovulation," "Hoogland Luteinized Unruptured Follicle," "Hoogland Active Follicle-Like Structure," or even "Hoogland Non-Active Follicle-Like Structure" – see Hoogland criteria above. The defining characteristic of dysfunctional ovulation is a low progesterone production in luteal phase.

The significance of low luteal progesterone production for embryo survival has been extensively documented by multiple infertility researchers.[28,29,30,31,32,33] Although there is no current consensus on an absolute minimum level of midluteal progesterone needed for embryo survival, low levels of mid-luteal serum progesterone are associated with an excess embryo loss.[34] Yding[35] found "that a minimum mid-luteal progesterone threshold of approximately 80-100nmol/L exists, which, when surpassed, results in reduced early pregnancy loss and in increased live birth rate" after IVF treatment, and luteal phase progesterone support is standard in IVF cycles to increase the implantation

and survival rates of transferred embryos.

These results are intuitively obvious, as progesterone mediates most of the genomic changes in the endometrium that must occur for implantation and placentation to occur.[36.37] Insufficient or mistimed progesterone production leads to an endometrial environment which decreases changes of implantation and survival. Interference with progesterone-dependent blastocyst adhesion and other steroid-dependent changes which mark endometrial receptivity is a recognized mechanism for "an interceptive approach to prevent embryo implantation."[38] Such "interception" could result either from direct actions of progestins on the endometrium and/or disruption of the timing or amount of luteal progesterone in relationship to follicle rupture.

3. Area under the curve of LH surge and luteal phase progesterone production

Since LH stimulation of granulosa cells results in luteinization and subsequent progesterone production, the amount and timing of the LH surge is critically important to sufficient progesterone production during the luteal phase. Croxatto's definition of dysfunctional ovulation would be exactly the type of ovulatory process which would produce a subsequent luteal phase deficiency syndrome, as Croxatto identifies by serum P levels less than or equal to 12nmol/L. Such "dysfunctional ovulations" are seldom accompanied by embryonic survival to achieve a positive pregnancy test at the end of a cycle, and these are precisely the ovarian activity which most concerns the patient and medical professional concerned with embryonic life.

The extensive literature on Luteal Phase Defect as a cause of recurrent pregnancy loss testifies to the excess embryo loss under conditions of low progesterone production even in clinically recognized pregnancies. The syndrome of blunted LH secretion is characteristic of a significant number of cycles studied during the use of hormonal contraceptives.

In summary, Hoogland Scoring is designed with the end point of predicting contraceptive failure rates, i.e., the number of embryos who survive to positive pregnancy test at the end of a cycle. Hoogland Scoring is not designed to exclude the potential for ovum release or embryo formation. Despite the clear potential for false negatives, many contraceptive researchers in past decades have relied upon lack of Hoogland "ovulation" as evidence for lack of egg release during the use of a particular contraceptive. It is noteworthy that other more recent researchers have simply used the presence of follicles >13mm as evidence of potential ovulatory activity, and not relied upon mid-luteal progesterone to exclude ovum release.

Q *What are the possible mechanisms of action of contraceptives without embryocidal activity?*

1. **"No egg release" theory**

(Discussed above under Hoogland ovulation and below in detail for different contraceptive methods)

2. **"Unfertilizable egg" theory**

There is no evidence demonstrating that the eggs released by women taking combined hormonal contraceptives cannot be fertilized, and in fact, the infertility literature reveals that egg retrieval during the use of combined hormonal contraceptive pills to time egg retrieval yields eggs which fertilize at least as often as eggs in spontaneous cycles.[39]

3. **"Sperm can't penetrate the mucus" theory**

Progestins [LNG] can thicken the cervical mucus such that sperm find it more difficult to penetrate.[40] But this difficulty is not an absolute barrier to sperm penetration beyond the cervix, as illustrated by recent review papers[41,42] which looked at the effect of levonorgestrel (a progestin used commonly in hormonal contraceptives) on cervical mucus in levonorgestrel IUD users. The amount of levonorgestrel released at the level of the cervix in levonorgestrel IUD users is much greater than the effect seen with hormonal contraceptive pills of any type. So, these levonorgestrel IUD users should demonstrate the maximum amount of cervical mucus changes. However, sperm were still recovered from the fallopian tubes of these levonorgestrel IUD users, although the total number of sperm was reduced. The fact that sperm are found in the fallopian tubes provides direct evidence that sperm can pass through the supposed "hostile mucus" induced by levonorgestrel.

4. The "impotent sperm" theory

A fourth hypothesis is that perhaps the sperm won't be able to capacitate and fertilize an egg. However, there is no scientific support for this theory, and empirical evidence against it. One study looked at the effect of large doses of LNG (used as emergency contraception) on sperm capacitation, and found no effect.[43] Direct evidence that at least some sperm capable of fertilizing an egg can reach and fertilize an egg in OCP users is the 2-8% pregnancy rate per year in women who use combined hormonal contraceptives.

Q *What is the potential for embryo formation & post-ovulatory conditions with combined estrogen and progestin contraceptives?*

1. Combined Oral Contraceptives (COCs)

Combined hormonal contraceptives include: both monophasic and triphasic combined oral contraceptives (COCs) as well as patches, implants, and vaginal rings that contain both an estrogenic and progestin component. The estrogenic component of COCs interferes with FSH secretion. Sufficient estrogenic

component to result in complete suppression of follicular recruitment was present in early COCs, but is responsible for many of the pill's nasty side effects: blood clots, strokes, and increased risk of breast cancer, migraines, etc. Since the 1980s, manufacturers have gradually reduced the amount of estrogenic component used in order to decrease incidence of side effects. Today's modern pills contain 30 micrograms or less of estrogen, which is insufficient to completely prevent the ovaries from recruiting and maturing follicles.

The International ESHRE workshop summarized the mechanism of action of COCs:

> *This report addresses the balance of benefits and risks from changes in ovarian and endometrial function from hormonal contraception. The main mode of action of hormonal contraception is inhibition of ovulation, due chiefly to the dose of oestrogen in combined oral contraceptives. With 20ug doses of ethinyl oestradiol, follicular activity is more common so that contraception depends on suppression of the LH surge or disruption of the endometrial cycle.*[44]

A more recent 2012 medical journal article concurs:

> *The main contraceptive effect of combined oral contraceptives (COCs) is inhibition of the midcycle luteinizing hormone (LH) surge to prevent ovulation. However, several studies have shown that the percentage of ovulatory cycles in women using low-dose COCs range between 1.5% and 16.8%. With this high rate of ovulatory cycles in women taking COCs, we would expect the pregnancy rate with COC use to be much higher than the perfect use failure rate of 0.3% were there not other effective mechanisms of contraceptive action in addition to ovulation inhibition.*
>
> *Another potential mechanism of contraceptive action is the suppression of follicle-stimulating hormone secretion during the follicular phase of the cycle, thereby preventing follicular maturation; however, follicular development has been shown to occur in 23% - 90% of cycles in women using COCs. There are also many progestin-related mechanisms that likely contribute to the overall efficacy of the combined contraceptives, such as thickening of cervical mucus, impairment of tubal mobility and peristalsis, and effects on the endometrial lining, making it less suitable for implantation.*[45]

The relative frequency of particular mechanisms of action in particular patients has been hotly debated, and Hoogland criteria were developed in part to settle this debate. A 2008 review article[46] analyzed the published literature looking for [Hoogland] ovulation rates on the combined oral contraceptive pills (COCs).

> *Results: Many of the studies were hampered by inadequate ovulation criteria; however, the overall incidence of ovulation determined by the reports*

uncovered in the literature search was 2.0% [95% confidence interval (CI) 1.1-3.3] with COCs containing 30-35 µg ethinylestradiol (EE), 1.1% (95% CI 0.60-2.0) with 15-20 µg EE COCs, 4.6% (95% CI 2.8-6.9) with phasic COCs, 1.25% (95% CI 0.03-6.8) with Cerazette and 42.6% (95% CI 33.4-52.2) with traditional POPs.

A 2010 study[47] looked directly at the issue of "consistent users" and found that women who consistently took the pill every day without failure had an "ovulation" rate of 2.7%. However, if women missed pills ("inconsistent use"), their rate of "ovulation" increased to 38.5%. This rate is compared to women who did not use birth control pills at all, who had an ovulation rate of 66.7%. This study would imply that inconsistent use of the birth control pill would suppress even Hoogland ovulation in only about half of the cycles.

How many women qualified as "inconsistent users"? In one study, which used an electronic monitoring device to track pill usage, 57% of women missed an average of three pills or more per cycle.[48] In another study, 17% of women were inconsistent users based on measuring synthetic hormone levels in their blood.[49]

2. Combined patches and rings

Vaginal rings and patches provide a more continuous level of estrogen and are associated with similar or less ovarian follicle formation than pills, although fewer studies have been done on patches and rings than on pills. One small study found no Hoogland "ovulation" on either COCs or combined contraceptive vaginal rings, but this involved only 33 women.[50] Of note in that study, rate of "follicle formation" in the vaginal ring group was roughly half the rate of the pill group. In another study, designed to look at ovarian activity on the patch vs. pills, the authors state:

The patch regimens demonstrated a dose-response for ovulation suppression and cycle control. Presumed ovulation, determined on the basis of serum progesterone concentrations > or = 3 ng/mL in cycles 1 and 3, occurred in 6.2% (Ortho Evra) and 7.2% (Ortho-Cyclen) of subjects.[51]

A recent review of all types of combined hormonal contraceptives noted that although ovulation is not common,

…among women who did ovulate, cycles were usually abnormal (i.e., low progesterone levels, small follicles and/or poor cervical mucus).[52]

Most of the research using the Hoogland scoring system to determine ovulation (follicular rupture + above threshold progesterone level in mid-luteal phase) reported a high incidence of low luteal phase progesterone levels in cases of sonographically determined follicular rupture, consistent with an induced luteal phase defect, in women who were documented with normal follicular rupture and adequate luteal phase progesterone prior to the start of the hormonal contraceptive.[53]

Q *What is the potential for embryo formation & post-ovulatory conditions with continuous progestin-only contraceptives?*

The mechanism of action of continuous progestin-alone contraception is well summarized in this review:

> *Modeled after the naturally occurring hormone progesterone, progestins are the synthetic hormones used in Norplant, depot-medroxyprogesterone acetate (DMPA), and progestin-only pills (POPs). Progestin-only contraceptives alter a woman's hormonal balance. In so doing, progestin-only contraceptives block a series of chemical signals essential to the completion of a normal reproductive cycle, either by blocking the release of an egg or by making its fertilization and implantation within the uterus unlikely. In many women, progestin-only contraceptives stop the monthly release of an egg. Even if an egg is released, progestin makes its movement through the fallopian tubes into the uterus more difficult. Progestin also thickens the mucus in the cervix, which stops sperm from penetrating the mucus and reaching an egg. In the unlikely even that ovulation does occur and an egg becomes fertilized, the hormonal disruption makes the lining of the uterus inhospitable for implantation. This multiple mode of action therefore makes progestin-only methods among the most reliable of all contraceptives. Norplant and progestin-only injectables have failure rates of less than 1%, while POPs are typically 95% effective.*[54]

The continuous progestin-only group includes:

1. Progestin-only pills ("mini-pills," POPs)
2. Implants (Nexplanon)
3. Injections (Depo-Provera)

[The topics of Progestin IUDs and progestin as emergency contraception will be discussed separately.]

By eliminating estrogen and using only a progestin, the major health problems seen with COCs – strokes, heart attacks, blood clots, liver problems, migraines, and other estrogen-related complications – are no longer a problem. However, estrogen stabilization of the endometrial lining is absent. Progestin-only contraceptives induce a thin friable endometrium which easily bleeds, and this is a common reason for discontinuation. In addition, the long-term use of progestin-only implants and injectables has been associated with significant loss of bone density, especially in young women.

1. **Progestin-only Pills**

The ESHRE Capri Workshop Review states that for women using the progestin-only pill:

> *Some 10% to a maximum of 15% of women will have complete inhibition of ovarian activity and*

these women will of course be amenorrheic. Around 50% of women tend to have regular ovulatory cycles with a normal luteal phase and these women will have a normal menstrual bleeding pattern. The remaining 35-40% will have inconsistent suppression of ovarian activity with variable follicular development and occasional ovulation often characterized by short or inadequate luteal phases.[55]

Many other studies confirm a high incidence of ovulation on POPs which use levonorgestrel,[56,57,58,59] though there may be a slightly lower incidence of Hoogland ovulation with desogestrel[60,61] and dienogest.[62]

2. Progestin implants (Norplant, Implanon, Nexplanon)

Progestin implants also result in a significant number of dysfunctional ovulations:

Sonographic and hormonal evidence of ovulation were observed in one third of Norplant users; two of them resulted in conception. However, the majority of these ovulatory cycles showed low midcycle peaks of E2, FSH, and LH and evidence of luteal phase defect (LPD).[63]

Another study[64] of ovulation in Norplant users showed…

…the frequency of cycles with luteal activity (ovulation) was 12% during the first 2 years, increasing to 44% in the latter years…

Breakthrough ovulation happens more frequently the longer Norplant is in place. One study of the 68mg etonorgestrel implant (Nexplanon) reported that 60% of cycles had ovarian follicles which were larger than 5mm.[65]

3. Injections (Depo-Provera)

Depo-Provera generally provides profound suppression of ovulation after the first month of use. However, ovulation can occur roughly a third of the time in the first month of injection if the initial Depo-Provera injection is given after day 7 of the menstrual cycle.[66] When the injectable progestins wear off, ovulation returns before fertility returns,[67] indicating a potential for ovulation with defective luteal phase.[68]

In summary, with the exception of Depo-Provera, a significantly greater number of women appear to have follicle rupture with the progestin-only contraceptives than with combined hormonal contraceptives. In order to explain the efficacy of progestin-only contraceptives, mechanisms of action other than preventing the release of eggs must play a major part in the mechanism of action. Just as with COCs, the potential effect on embryos created during the use of progestin-only contraceptives are:

a. interference with tubal peristalsis,

b. the effect of the progestin on the LH surge before ovulation and the resultant decreased progesterone

production by the corpus luteum after ovulation, and

c. the changes that happen in the cells of the endometrium when progestins interfere with the progesterone-mediated transcription which prepares the endometrium for implantation.

a. Interference with tubal peristalsis

Since embryos are created in the fallopian tubes, the effect of progestins on the tubal environment is potentially significant. Progestin-only contraceptives interfere with progesterone-depended peristalsis and ciliary beat frequency.[69] The result of this interference is slowing of tubal transport, and mis-timing of the arrival of the embryo into the endometrial cavity outside of the implantation window. Women on continuous progestin-only contraceptives, with the exception of Depo-Provera users,[70] are at increased risk of ectopic pregnancy.[71] With the levonorgestrel implants (Norplant), the risk is five times as high for ectopic pregnancy.[72]

b. Effects on LH release and luteal progesterone production

Progestin-only contraceptives interfere with the amount of LH produced by the pituitary[73] and decreases the LH surge. If the LH surge is sufficient to allow ovulation, the corpus luteum formed often makes abnormally low amounts of progesterone.[74] Other studies suggest a decreased LH surge when a breakthrough ovulation takes place on progestin-only contraceptives,[75] and subsequent insufficient luteal function[76] as was discussed under the section on combined hormonal contraceptives.

c. Endometrial changes

The effect of progestin-only contraceptives on the endometrium was reviewed and summarized in the ESHRE Capri Workshop Group paper entitled, "Ovarian and Endometrial Function during Hormonal Contraception":[77]

> *There is some evidence for significant change in the morphology of the endometrial vessels in women exposed to long acting progestogens. There is a reduction in numbers of the spiral arteries, sizes and the degree of spiraling. However, the main change seems to be in the capillaries and venules. Endometrial microvascular density is increased, perhaps creating more opportunities for breakthrough bleeding in women exposed to high and medium doses of progestogen. There is also evidence for an increase in the fragility of the superficial venules. Exogenous steroids may disrupt the normal tightly controlled relationship between the growth of endothelial cells and the capillaries and the glandular and cellular components of the endometrium.*
>
> *There may be changes in endometrial vascular constriction and dilation and there is evidence for alterations of the synthesis and secretion of endothelin and a variety of protanoids in the endometrium of progestogen users. Also described are substantial increases of several types of migratory leukocytes which have the potential for*

releasing a wide range of destructive as well as angiogenic and repair molecules within the endometrium. There may be changes in endometrial haemostatic mechanisms, such as alterations in tissue fibrinolytic activity and platelet function. There may also be disturbances of mechanism involved with endometrial repair or changes in angiogenic or endothelial growth factors.

All of these changes may be inter-related and may be due to a direct effect of the progestogen on the endometrium or may result from changes in the functional status of steroid receptors, rendering the endometrium "unresponsive to ovarian steroids."

Other papers describe similar structural and functional changes in the endometrium after exposure to progestins.[78,79,80,81,82,83,84,85,86] But the endometrial disturbance seen with progestin-only contraceptives are more profound than the changes induced by COCs.

The significance of progestins "rendering the endometrium unresponsive to ovarian steroids" is great. Even in the face of a normal LH surge, and even with normal progesterone production in a particular cycle, the progestin itself directly renders the endometrium "unable to respond to ovarian steroids" and thus unable to prepare for implantation.

There are no direct studies looking at miscarriage rate on the progestin-only contraceptives. However, the few studies suggesting an increased loss rate for women after use of combined hormonal contraception implicate the progestin component of the COC. Progestins cause profound changes and atrophy of the endometrium, changes which may take some time to resolve after discontinuing progestin-only contraceptives. Support for this idea is the known delay in return to fertility, i.e., the delay in being able to achieve and sustain a positive pregnancy test, for several months after the long-term use of continuous progestin-only contraceptives.

Q What is the potential for embryo formation and post-ovulatory conditions for copper and LNG-IUDs?

In discussing how IUDs can so effectively prevent a positive pregnancy test at day 28 of the cycle, a 1990 review article states:

Implantation is prevented by endometrial changes resulting from both the presence of the device and the copper ions (Hawkins and Elder, 1979). Inert IUCDs may be less effective in preventing implantation and being larger are less easy to insert into a nulliparous uterus; hence copper IUCDs are used preferentially. Implantation occurs some six days following ovulation and this IUCD insertion may be used up to six days after coitus, although insertion beyond this time may still be effective (Rowlands and Guillebaud, 1981). In their review of published studies, Fasoli et al. (1989) report only one pregnancy in a total of 879 IUCD insertions and this pregnancy

was presumed to have been resolved by a spontaneous abortion. The overall failure rate is quoted as 0.1%.[87]

The IUD is a piece of metal or plastic of various different shapes which is placed inside the endometrial cavity and comes in direct contact with the endometrial lining. The presence of the IUD sets up a chronic inflammation in the endometrial lining. An alternative formulation, the progestin-IUD, delivers a high concentration of levonogestrel at the level of the endometrium and thus has the additional actions of thickening of cervical mucus, and slowing of tubal mobility.

It has been known for decades that an IUD causes the lining of the uterus to become inflamed, decreasing the capacity of the endometrium to allow the embryo to complete implantation. This inflammatory mechanism is clearly embryocidal because embryos who do not implant after reaching the endometrial cavity die. When the initial research into IUD mechanisms of action was published in the 1980s, many women opted for other methods less clearly embryocidal. IUD popularity fell even more drastically subsequent to the Dalkon Shield class action lawsuits, from IUD users with pelvic infections resulting in infertility and other complications. However, IUDs continued to be marketed, albeit with little research into either mechanism of action or long-term effects on women. A 2008 article summarized the state of research with IUDs with remarkable honesty:

Moreover, if it was conclusively shown that the sole or principal mode of action was to prevent the embryo from implanting, then this method, as in the case with emergency contraception, would be considered by the Roman Catholic church as causing an early abortion. As a result, many agencies involved in the research, development or delivery of contraception prefer to leave the mechanism of action issue unresolved, which may explain why research into the contraceptive mechanisms of IUDs has been sparse in the last 20 years.[88]

There is sufficient evidence to suggest that IUDs can prevent and disrupt implantation. The extent to which this interference contributes to its contraceptive action is unknown. The data are scanty and the political consequences of resolving this issue interfere with comprehensive research.[89]

However, the use of IUDs has been resurrected in the past decade, for numerous reasons beyond the scope of this article. As part of the public relations effort to market the IUD, researchers often published dramatic verbal spin to obscure what is known about the effects of the IUD on the embryo or denied the significance of embryocidal mechanisms of action as, for example, in this 1997 review article which states: *"The prevention of pregnancy before implantation is contraception and not abortion."*[90]

Claims that the LNG-IUD worked mostly by preventing sperm transport or by suppressing ovulation were not confirmed by research designed to specifically test

these hypotheses. One 1995 article stated clearly:

> *Our previous study in LNG-IUD users in their fourth year of use demonstrated that, according to progesterone levels, 88% of the cycles studied were ovulatory. However, normal follicular growth and rupture was observed in only 53% of these cycles. Pre-ovulatory estradiol, LH and mid-luteal progesterone levels were lower in LNG-IUD users compared with the controls.*[91]
>
> *The presence of good cervical mucus was observed in 69% of the ovulatory cycles studied in the LNG-IUD users. This indicates that effects on cervical mucus cannot be the main mechanism of action of the LNG-IUDs. It is concluded that LNG-IUDs may exert a contraceptive effect in many different ways, such as inhibition of ovulation, endometrial changes preventing implantation, alteration of physical and chemical properties of cervical mucus affecting sperm transport and subtle disturbances in hypothalamic pituitary ovarian function, resulting in alterations of follicular development and rupture.*[92]

Most of the recent spin is accomplished by the use of the term "fertilized egg" as a substitute term for the biologically correct term "embryo," and by using implantation to define the beginning of "pregnancy." Embryos in transit to the uterus and who have not implanted are called "fertilized eggs." The rhetorical significance of preventing a "fertilized egg" from implanting is significantly different than the reality of preventing implantation of a human embryo.

A recent review article[93] on "emergency contraception" describes the use of IUDs for EC:

> <u>*Copper-bearing IUDs*</u>
>
> *Implantation occurs 6-12 days following ovulation. Therefore, copper IUDs can be inserted up to 5 days after ovulation to prevent pregnancy. Thus, if a woman had unprotected intercourse three days before ovulation occurred in that cycle, the IUD could prevent pregnancy if inserted up to 8 days after intercourse.*

As we analyze this paragraph, knowing that fertilization takes place within hours of ovulation, we can see that IUDs placed *5 days after ovulation* can only work by a mechanism which destroys the embryo prior to the production of a positive pregnancy test.

A careful examination of IUD research demonstrates that:

> 1) IUDs do not prevent ovulation. Women release eggs only a little less often than normal, even on the LNG-IUD.[94,95,96,97]
>
> 2) The LNG-IUD can interfere with the corpus luteum production of progesterone, which in turn interferes with the normal development of the endometrium, which in turn leads to an endometrium unable to accept an implantation and ability to sustain an embryo which has implanted.[98]

3) Although IUDs can decrease the absolute number of sperm which reach the fallopian tubes,[99] sperm are still capable of reaching the fallopian tube in copper IUDs and LNG-IUDs, and have been directly observed and recovered from the tubes of women using IUDs.[100,101,102]

4) Fertilizations do take place in IUD users. Embryos have been directly recovered from the fallopian tubes of IUD users.[103,104] In addition, the documented pregnancy rate of 0.1% proves that embryos can be created during the use of the IUD.

5) Embryos created during the use of the copper IUDs develop abnormally either due to toxic effects of the copper on sperm, or toxic effects on the egg, or direct toxicity to the embryo.[105,106,107,108]

6) The IUD changes the lining of the uterus, making implantation difficult. This is one of the most widely documented mechanisms of action of both copper IUDs and Progestin IUDs.[109,110,111,112,113,114,115,116,117]

7) Pregnancies diagnosed during the use of the IUD are more frequently in the fallopian tubes [ectopic pregnancies],[118,119,120] giving evidence that the embryos which survive to enter the uterus are selectively "lost."[121]

8) IUDs have been used as "emergency contraception" and are recommended for use in situations where ovulation has already occurred, and the woman is late in her cycle.[122] IUDs placed after day 24 (after implantation has already taken place) are "effective" in preventing a positive pregnancy test, and that effectiveness must by definition involve embryocidal actions because embryos are created by day 14.

In summary, the IUD has been well documented to act after fertilization, causing embryo death. Attempts to minimize the significance of this major mechanism of action have focused on renaming the early embryo by calling it a "fertilized egg" and by claiming that death of human embryos before implantation is not "abortion." Regardless of terminology, IUDs clearly can cause the death of embryos both before and after implantation, and this is likely their major mechanism of action.

Q What is the potential for embryo formation and post-ovulatory conditions with emergency contraceptives?

Emergency contraceptives include both high dose progestins (Plan B, Next Choice) as well as progesterone receptor antagonists RU-486 (Mifeprex) and ulipristal (Ella). Both high dose progestins and the progesterone receptor antagonists have variable mechanisms depending on the timing of administration in relationship to the LH surge and ovulation.

1. Preventing the release of eggs

Both high dose levonorgestrel (Plan B) and single dose RU-486 (Mifeprex) and single dose ulipristal (Ella) can delay or inhibit

follicular rupture if taken 4 to 1 day prior to the onset of the LH surge. However, the efficacy in preventing ovulation decreases as the LH peak nears. Many studies show that if LNG (Plan B) is taken before ovulation, specifically between 4 to 2 days before the LH peak, then Plan B can delay ovulation for several days or prevent ovulation altogether.[123,124,125] However, if LNG is given after LH begins to rise (one day before the LH peak) or given on the day of the LH peak, then egg release is not reliably prevented.[126,127,128]

2. Inhibition of LH peak if taken after the onset of the LH surge

If Plan B or Ella are taken after the onset of the LH surge, egg release will still occur,[129,130,131,132] but the LH surge will be decreased. As discussed previously, an inadequate LH surge will result in a corpus luteum producing inadequate amounts of progesterone to mature the endometrial lining, or to sustain an embryo after implanting.[133,134,135,136,137,138]

In addition to decreasing the LH surge, both ulipristal (Ella) and RU-486 (Mifeprex) can directly block the ability of the corpus luteum to produce progesterone.[139] One review article states:

> *There is better evidence of an effect of mifepristone on the corpus luteum; when given in the mid-luteal or late luteal phase of the cycle, it induced regression of the corpus luteum in about 50 percent of women.*[140]

3. Effect of high dose progestins (Plan B) or progesterone blockers (Ella, RU-486) on fertilization

There is no evidence that either high dose progestins or progesterone blockers prevent fertilization. In fact, the evidence shows that neither high dose progestins[141,142,143,144,145] nor progesterone blockers[146,147] interfere with sperm function or fertilization. One review of EC states bluntly: "There is no direct evidence that any of the hormonal methods of emergency contraception prevent fertilization…"[148]

4. Effect of high dose progestin (Plan B) or progesterone blockers (Ella, RU-486) on transport of the embryo through the fallopian tube

Plan B does not appear to change the function of the fallopian tubes.[149]

Ella causes a significant effect on tubal function, blocking progesterone receptors in the tube[150] and thus blocking the effects of progesterone. The sweeping action of the tube responds to progesterone and estrogen, so it is possible that the transport of the embryo through the tube is changed, resulting in the embryo reaching the uterus at a time in which implantation is more difficult.[151,152]

5. The effect of high dose progestin (Plan B) or progesterone blockers (Ella, RU-486) directly on the endometrium

High dose progestin (Plan B)

Although changes in the endometrium with high dose progestins are not as dramatic as with progesterone blockers like Ella, high dose progestins like Plan B can cause endometrial changes which can make implantation more difficult.[153,154]

Progesterone blockers (Ella and RU-486)

Progesterone blockers directly block the effects of progesterone on the cells of the endometrial lining. So the changes that progesterone must make in the lining to allow the embryo to implant are directly blocked by progesterone blockers, resulting in an endometrium which does not allow for implantation.[155,156,157,158,159]

6. Effect of high dose progestin (Plan B) or progesterone blockers on an implanted embryo

Administration of Plan B after ovulation does not result in a decrease in expected pregnancies, and has not been demonstrated to have an effect on pregnancies which do take place and go to term. There does not appear to be any increase in miscarriage rate for pregnancies diagnosed after the use of Plan B.

In contrast, progesterone blockers are very effective in inducing abortion. RU-486, if taken after implantation, effectively blocks the effect of progesterone both directly at the level of the maternal decidua and also has a direct blockade at the level of the corpus luteum, preventing production of ovarian progesterone.

Ella is equipotent with RU-486 and is a derivative of RR-486, so we would reasonably expect that at equal doses Ella would abort implanted embryos. Further evidence of this is the very high efficacy of Ella when taken at any time during the cycle. This embryocidal activity resulted in the European Medicines Agency (EMEA) statement that ulipristal can cause the death of embryos.[160]

A review article on Ella[161] for pharmacists states:

> *The mechanism of action of ulipristal in human ovarian and endometrial tissue is identical to that of its parent compound mifepristone.[162,163] Unlike mifepristone, which is provided directly by clinics and physicians' offices, ulipristal will be available by prescription. The European Medicines Agency (EMEA) states that ulipristal is embryo-lethal.[164] However, only limited safety and reproductive toxicology studies have been performed with ulipristal, despite Internation Conference on Harmonization Good Clinical Practice (ICHGCP) requirements.[165] Nevertheless, the results form the existing studies in animals are instructive in terms of the potential abortive effects of the drug in humans. In Macaque monkeys, intramuscular administration of ulipristal acetate 0.5 mg/kg resulted in a loss of 4 of 5 fetuses.[166]*

The article cites the European Medicines Agency report for EllaOne showing the effects of single oral doses of ulipristal on early pregnancy in rats[167] and Macaque monkeys[168] and continues:

> *The human dose equivalents are normalized to body surface area. Based on body surface area, the human dose is similar to the abortive dose in rats and between the no effect and abortive dose in monkeys. The human dose is*

about 4-fold lower than the abortive dose in monkeys. Based on animal data, it is generally accepted that at least a 10-fold margin is required to establish safety in humans. Based on these data, it can be reasonably expected that the prescribed dose of 30 mg of ulipristal will have an abortive effect on early pregnancy in humans.

What this means for women who take Ella is that the dose of Ella sold as "emergency contraception" is capable of producing enough progesterone blockade to kill an early embryo who has already implanted. This dose is also sufficient to prevent the embryo from implanting.

The review article[169] goes on:

Further experience with abortion in humans is supplied by the two Phase 3 trials submitted to the FDA for approval. Two of these trials provided information on pregnancies after ulipristal administration. In the first, 5 of 6 pregnancies with known outcomes ended in "miscarriage" for women who did not choose to abort.[170] And in the second, 4 of 6 women "miscarried," and the remaining 2 were lost to follow-up.[171] Although the exceedingly small numbers are inadequate for any power analysis of effectiveness, the high rate of fetal demise in known outcomes highlights the need for a mandatory fetal registry of ulipristal failures. Given the drug's effectiveness at causing fetal demise, as seen in the clinical trials supporting FDA approval, it is likely that off-label use of ulipristal for termination of pregnancy will soon follow commercial availability.

So the studies submitted to the FDA demonstrated that there was an extremely high rate of "miscarriage" in the 5% of women in the study whose embryos survived long enough to produce a positive pregnancy test, but could not survive the prolonged progesterone blockade caused by Ella. These numbers demonstrated that Ella is able to cause embryos to die after implantation.

Summary of Recommendations and Conclusion

The purpose of this Committee Opinion is to summarize what is currently published in the medical literature regarding the possibility of embryo formation during the use of various methods of contraception. The committee publishes this bulletin as an aid to the informed consent process prior to prescribing the use of contraceptives, and not as a constraint on individual member practice.

The following recommendations are based on good and consistent scientific evidence (Level A):

1. Women should be informed of all of the mechanisms of action of each of the contraceptive methods as part of informed consent.

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