ProLifeOB|GYNS Committee Opinion 7

American Association *of* Pro-Life
Obstetricians *&* Gynecologists

Professional Ethics Committee of AAPLOG

Embryocidal Potential of Modern Contraceptives

The mechanism of action of contraceptive drugs and devices forms 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 of current research. AAPLOG members take different positions on the issue of contraception per se. 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.

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

I. Background

   A. Brief review of Reproductive Physiology
   B. Clarification of Terminology
   C. Egg release vs Hoogland "ovulation"
   D. Possible Mechanisms of Action of Contraceptives Without Embryocidal Activity

[1] Rivera R, Yacobson I, Grimes D. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. Am J Obstet Gynecol 1999; 181: 1263-9. At p 1267.

II. Hormonal contraception
    A. Combined Estrogen and Progestin
    B. Progestin Only

III. Copper IUD (Cu IUD) and Levonorgestrel IUD (LNG IUD)

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V. Summary and Conclusions.

I. Background

A. 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 are: (cycle days approximate)

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:

[2] Condic ML. When does human life begin? The scientific evidence and terminology revisted. Univ of St. Thomas J of Law and Public Policy (2013) 8 (1) Article 4 p44-81.

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 the endometrial cavity .[4] [5] These progesterone mediated changes provide for an optimal window of implantation corresponding to the time when the embryo arrives into the endometrial cavity. The normal endometrial lining

[3] Harrison D, Buskmiller C, Chireau M, Ruppersberger LA, Yeoung PP. Systematic review of ovarian activity and potential for embryo formation and loss during the use of hormonal contraception. Linacre Quarterly 2018, Vol. 85(4) 453-469.
[4] Riesewijk A, Martin J, van Os R, Horcajadas JA, Polman J, Pellicer A, Mosselman S, and Simon C. Gene expression profiling of human endometrial receptivity on days LH+2 versus LH+7 by microarray technology. Mol. Hum. Reprod. (2003) 9 (5): 253-264. doi: 10.1093/molehr/gag037
[5] W.A. Castro-Rendón, J.F. Castro-Álvarez, C. Guzmán-Martinez, J.C. Bueno-Sanchez. Blastocyst-endometrium interaction: intertwining a cytokine network Brazilian Journal of Medical and Biological Research (2006) 39: 1373-1385

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 requires 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.

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[6] Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update, Vol.12, No.6 pp. 731–746, 2006

[7] Achache H, Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update, Vol.12, No.6 pp. 731–746, 2006

[8] Rytkönen KT, Erkenbrack EM, Poutanen M, Elo LL, Pavlicev M, Wagner GP. Decidualization of Human Endometrial Stromal Fibroblasts is a Multiphasic Process Involving Distinct Transcriptional Programs. Reprod Sci. 2019 Mar;26(3):323-336. Epub 2018 Oct 11. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4354233/pdf/jrd-61-067.pdf

[9] Niinimaki M, Ruokonen A, Tapanainen JS, Jarvela IY. Effect of mifepristone on the corpus luteum in early pregnancy. Ultrasound Obstet Gynecol2009;34: 448 – 453. Available at: https://obgyn.onlinelibrary.wiley.com/doi/epdf/10.1002/uog.6418

[10] Hirata R, Hojo T, Sano M, Hayashi N, Okuda K, Potential role of hCG in apoptosis of human luteinized granulosa cells. J. Reprod. Dev. 61: 67–73, 2015

[11] Carrascosa JP, Cotán D, Jurado I, Oropesa-Ávila M, Sánchez-Martín P, Savaris RF, Tan J, Sánchez-Alcázar JA, Tan SL, Horcajadas JA. The Effect of Copper on Endometrial Receptivity and Induction of Apoptosis on Decidualized Human Endometrial Stromal Cells. Reprod Sci. 2018 Jul;25(7):985-999. Epub 2017 Oct 5.

[12] Kim CR, Matrinez-Maza O, Magpantay L, Magyar C, Gornbein J, Rible R, Sullivan P. Immunologic evaluation of the endometrium with a levonorgestrel intrauterine device in solid organ transplant women and healthy controls. Contraception 94 (2016) 534–540. Available at: https://www.contraceptionjournal.org/article/S0010-7824(16)30140-8/pdf

[13] Shanmugasundaram U, Hilton JF, Critchfield JW, Greenblatt RM, Gludice LC, Averbach S, Seidman D, Shacklett BL, Smith-McCune K. Effects of the levonorgestrel-releasing intrauterine device on the immune microenvironment of the human cervix and endometrium. Am J Reprod Immunol. 2016 August ; 76(2): 137–148. doi:10.1111/aji.12535. available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5316474/pdf/nihms844758.pdf

B. 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 1960's the term conception was used in the legal, lay and medical literature synonymously with the term "fertilization" ie sperm egg fusion. However, in the 1960's 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, as 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.

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[14] American College of Obstetricians and Gynecologists. **Terminology bulletin no. 1: terms used in reference to the fetus.** The College, Chicago; 1965.
[15] https://medical-dictionary.thefreedictionary.com/ovulation
[16] Harrison D, Buskmiller C, Chireau M, Ruppersberger LA, Yeung PP. Systematic review of ovarian activity and potential for embryo formation and loss during the use of hormonal contraception. Linacre Quarterly 2018, Vol. 85(4) 453-469.

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

C. ***Egg release vs Hoogland "ovulation"***

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 ie "***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 by far the more frequently used currently, 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 ie 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)", "Non-Active Follicle-Like Structure" and "No Activity".

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[17] Croxatto, H. B., V. Brache, M. Pavez, L. Cochon, M. L. Forcelledo, F. Alverez, R. Massai, A. Faundes, and A. M. Salvatierra. 2004. "Pituitary-ovarian Function Following a Standard Levonorgestre in Emergency Contraception Dose or a Single 0.75 mg Dose Given on the Days Preceding Ovulation." Contraception 70, no. 6: 442–50.

[18] Harrison D, Buskmiller C, Chireau M, Ruppersberger LA, Yeoung PP. Systematic review of ovarian activity and potential for embryo formation and loss during the use of hormonal contraception. Linacre Quarterly 2018, Vol. 85(4) 453-469.

[19] Hoogland, H. J., and S. O. Skouby. 1993. "Ultrasound Evaluation of Ovarian Activity under Oral Contraceptives." Contraception 47, no. 6: 583–90.

[20] Landgren, B. M., A. I. Unden, and E. Diczfalusy. 1980. "Hormonal Profile of the Cycle in 68 Normally Menstruating Women." Acta Endocrinologica 94, no. 1:89–96.

[21] Hoogland HJ, Skouby SO. Ultrasound evaluation of ovarian activity under oral contraceptives. Contraception (1993) 47: 583-590.

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 > 0.1 nmol/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 if 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 > 0.1 nmol/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 > 13 mm diameter
   2) Follicles may rupture or persist
   3) Serum estradiol level > 0.1 nmol/L
   4) Serum progesterone level < 5nmol/L in luteal phase.

d. "Hoogland Non-active Follicle-Like Structure" requires:
   1) Dominant follicle > 13 mm diameter
   2) Follicles may rupture or persist
   3) Serum estradiol < 0.1nmol/L
   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 preceeded by an LH peak, or preceeded 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.

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[22] Harrison D, Buskmiller C, Chireau M, Ruppersberger LA, Yeoung PP. Systematic review of ovarian activity and potential for embryo formation and loss during the use of hormonal contraception. Linacre Quarterly 2018, Vol. 85(4) 453-469.

[23] Check JH, Adelson HG, Dietterich C, Stern J. Pelvic sonography can predict ovum release in gonadotrophin-treated patients as determined by pregnancy rate. Human Reprod 1990 5(3): 234-236

[24] Liukkonen S, Koskimies AI, Tenhunen A, Ylöstalo P. Diagnosis of luteinized unruptured follicle (LUF) syndrome by ultrasound. Fertil Steril. 1984 Jan;41(1):26-30.

[25] Croxatto HB, Salvatierra AM, Fuentealba B, Massai R. Contraceptive potential of a mifepristone-nomegestrol acetate sequential regimen in women. Human Repro (1998); 13(12): 3297-3302.

[26] Birtch RL, Olatunbosun OA, Pierson RA. Ovarian follicular dynamics during conventional vs. continuous oral contraceptive use. Contraception 73(2006) 235-243.

[27] Coxatto HB, Brache V, Pavez M, Cochon L, Forcelledo ML, Alverez F, Massai R, Faundes A, Salvatierra AM. Pituitary-ovarian function following a standard levonorgestreln emergency contraception dose or a single 0.75 mg dose given on the days preceding ovulation. Contraception 70 (2004) 442-450.

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 an 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 chances 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

[28] Devoto L, Kohen P, Munoz A, Strauss JF. Human corpus luteum physiology and the luteal-phase dysfunction associated with ovarian stimulation. Reproductive BioMedicine Online Vol 18 Suppl.2.(2009) 19-24.
[29] Ozlu T, Gungor AC, Emine M. Duran DB. Use of progestogens in pregnant and infertile patients. Arch Gynecol Obstet(2012) 286: 495-503.
[30] Arce JC, Balen A, Platteau P, Pettersson G, Andersen AN. Mid-luteal progesterone concentrations are associated with live birth rates during ovulation induction. Reprod Biomed Online. 2011 May;22(5):449-56.
[31] Yding Andersen C1, Vilbour Andersen K. Improving the luteal phase after ovarian stimulation: reviewing new options. Reprod Biomed Online. 2014 May;28(5):552-9.
[32] Kaur R, Gupta K. Endocrine dysfunction and recurrent spontaneous abortion: An overview. Int J Appl Basic Med Res. 2016 Apr-Jun; 6(2): 79–83.
[33] Achache H and Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update, Vol.12, No.6 pp. 731–746, 2006.
[34] Arce JC, Balen A, Platteau P, Pettersson G, Andersen AN. Mid-luteal progesterone concentrations are associated with live birth rates during ovulation induction. Reprod Biomed Online. 2011 May;22(5):449-56.
[35] Yding Andersen C1, Vilbour Andersen K. Improving the luteal phase after ovarian stimulation: reviewing new options. Reprod Biomed Online. 2014 May;28(5):552-9.
[36] Achache H and Revel A. Endometrial receptivity markers, the journey to successful embryo implantation. Human Reproduction Update, Vol.12, No.6 pp. 731–746, 2006.
[37] Riesewijk A, Martin J, van Os R, Horcajadas JA, Polman J, Pellicer A, Mosselman S, Simon C. Gene expression profiling of human endometrial receptivity on days LH+2 versus LH+7 by microarray technology. 1. Mol. Hum. Reprod. (2003) 9 (5): 253-264.
[38] Riesewijk A, Martin J, van Os R, Horcajadas JA, Polman J, Pellicer A, Mosselman S, Simon C. Gene expression profiling of human endometrial receptivity on days LH+2 versus LH+7 by microarray technology. 1. Mol. Hum. Reprod. (2003) 9 (5): 253-264.

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 the 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 >13 mm as evidence of potential ovulatory activity, and not relied upon mid-luteal progesterone to exclude ovum release.

D. Possible mechanisms of action 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

[39] Mashiach S, Dor M, Goldenberg J, Shalev J, et al. Programmed oocyte retrieval: clinical and biological effects of oral contraceptives administered before in vitro fertilization. Gynecol. Endocrinol 3 ((1989) 107-115.
[40] Insler V, Glezerman M, Zeidel L, Bernstein D, Misgav N. Sperm storage in the human cervix: a quantitative study. Fertil Steril. 1980 Mar;33(3):288-93.
[41] Stanford JB and Mikolajczyk RT. Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects . Am J Obstet Gynecol 2002;187:1699-708 [Quoting Barbosa I, Olsson SE, Odlind V, Goncalves T, Coutinho E. Ovarian function after seven years' use of a levonorgestrel IUD. AdvContracept 1995;11:85-95.]
[42] The ESHRE Capri Workshop Group, Intrauterine devices and intrauterine systemsHuman Reproduction Update, Vol.14, No.3 pp. 197–208, 2008

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 was that perhaps the sperm won't be able to capacitate and fertilize and 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.

II. Hormonal contraceptives: potential for embryo formation and post ovulatory conditions.

A. Combined Estrogen and Progestin contraceptives

1. Combined Oral Contraceptives (COC)

Combined hormonal contraceptives include: both monophasic and triphasic combined oral contraceptives (COC's) as well as patches, implants and vaginal rings that contain both an estrogenic and progestin component. The estrogenic component of COC's interferes with FSH secretion. Sufficient estrogenic component to result in complete suppression of follicular recruitment was present in the early COC's, 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 1980's, 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 COC's:

"*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*

[43] Brito KS, Bahamondes L, Nascimento JA, de Santis L, Munuce MJ. The in vitro effect of emergency contraception doses of levonorgestrel on the acrosome reaction of human spermatozoa.Contraception. 2005 Sep;72(3):225-8.

> *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 ranges 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 (COC's).

> "*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 take 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 in about half of the cycles.

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[44] ESHRE Capri Workshop Group "Ovarian and Endometrial function during hormonal contraception" Human Reproduction Vol 16, No.7 pp. 1527-1535, 2001.

[45] Steward R, Melamed A, Granat A, Michell DR Jr. Comparison of cervical mucus of 24/4 vs. 21/7 combined oral contraceptives. Contraception 86 (2012) p.710-715.

[46] Milsom I, Korver T, Ovulation incidence with oral contraceptives: a literature review. J Fam Plann Reprod Health Care 2008; 34(4): 237–246.

[47] Westhoff CL, Torgal AH, Mayeda ER, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use. Obstet Gynecol. 2010; 116:275–283.

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 3 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 COC's 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

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[48] Hou MY, Hurwitz S, Kavanagh E, Fortin J, Goldberg AB. Using daily text-message reminders to improve adherence with oral contraceptives: A randomized controlled trial. Am J Obstet and Gynecol. 2010; 116:633–640. As quoted in Petrie KA, Torgal AH and Westhoff CL Matched-paires analysis of ovarian suppression during oral versus vaginal hormonal contraceptive use. Contraception. 2011 November ; 84(5): e1–e4. doi:10.1016/j.contraception.2011.05.003.

[49] Westhoff CL, Torgal AH, Mayeda ER, et al. Ovarian suppression in normal-weight and obese women during oral contraceptive use. Obstet Gynecol. 2010; 116:275–283.

[50] Petrie KA, Torgal AH, Westhoff CL. Matched-pairs analysis of ovarian suppression during orgal versus vaginal hormonal contraceptive use. Contraception. 2011 November ; 84(5): e1–e4. doi:10.1016/j.contraception.2011.05.003

[51] Dittrich R, Parker L, Rosen JB, Shangold G, Creasy GW, Fisher AC; Ortho Evra/Evra 001 Study Group. Transdermal contraception: evaluation of three transdermal norelgestromin/ethinyl estradiol doses in a randomized, multicenter, dose-response study. Am J Obstet Gynecol. 2002 Jan;186(1):15-20.

[52] Zapata LB, Steenland MW, Brahmi D, Marchbanks PA, Curtis KM. Effect of missed combined hormonal contraceptives on contraceptive effectiveness: a systematic review. Contraception. 2013 May;87(5):685-700. doi: 10.1016/j.contraception.2012.08.035. Epub 2012 Oct 22.

follicular rupture and adequate luteal phase progesterone prior to the start of the hormonal contraceptive.[53]

B. 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 event 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", POP's)
2. Implants (Norplant, Implanon)
3. Injections (Depo-Provera)

[The topics of Progestin IUD's and Progestin as Emergency Contraception will be discussed separately]
By eliminating estrogen, and using only a progestin, the major health problems seen with COC's -strokes, heart attacks, blood clots, liver problems, migranes 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.

There is much more reason for concern about embryo formation and loss with progestin-only contraceptives than with combined hormonal contraceptives because of the much greater

[53] Harrison D, Buskmiller C, Chireau M, Ruppersberger LA, Yeoung PP. Systematic review of ovarian activity and potential for embryo formation and loss during the use of hormonal contraception. Linacre Quarterly 2018, Vol. 85(4) 453-469.
[54] Keller S.Progestin-only methods are very effective.Netw Res Triangle Park N C. 1995 Jun;15(4):4-8.

incidence of sonographically documented follicular rupture in users of progestin only contraceptives.

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 POP's 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)

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.

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[55] EsHRE Capri Workshop Group Ovarian and endometrial function during hormonal contraception. Human Reprod [2001] 16 (7); 1527-1535

[56] Milsom I, Korver T. Ovulation incidence with oral contraceptives: a literature review.J Fam Plann Reprod Health Care 2008; 34(4): 237–246

[57] Keller S.Progestin-only methods are very effective.Netw Res Triangle Park N C. 1995 Jun;15(4):4-8.

[58] Rivera R, Yacobson I, Grimes D. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. Am J Obstet Gynecol 1999; 181 (5) Part I 1263-1269

[59] Bayle B The antinidatory activity of oral contraceptives Contracept Fertil Sex (Paris). 1994 Jun;22(6):391-5.

[60] Milsom I, Korver T. Ovulation incidence with oral contraceptives: a literature review.J Fam Plann Reprod Health Care 2008; 34(4): 237–246.

[61] Korver T, Klipping C, Heger-Mahn D, Duijkers I, van Osta G, Dieben T. Maintenance of ovulation inhibition with the 75-microg desogestrel-only contraceptive pill (Cerazette) after scheduled 12-h delays in tablet intake. Contraception. 2005 Jan;71(1):8-13.

[62] Klipping C, Duijkers I, Remmers A, Faustmann T, Zurth C, Klein S, Schuett B. Ovulation-Inhibiting Effects of Dienogest in a Randomized, Dose-Controlled Pharmacodynamic Trial of Healthy Women Journal of Clinical Pharmacology, 2012;52:1704-1713.

[63] Shaaban MM, Segal S, Salem HT, Ghaneimah SA, Khalifa EA, Ahmed AG.Sonographic assessment of ovarian and endometrial changes during long-term Norplant use and their correlation with hormonal levels.Fertil Steril. 1993 May;59(5):998-1002.

[64] Brache V, Alvarez-Sanchez F, Faundes A, Tejada AS, Cochon L. Free levonorgestrel index and its relationship with luteal activity during long-term use of Norplant implants. Adv Contracept. 1992 Dec;8(4):319-26.

One study of Implanon users reported that 60% of cycles had ovarian follicles which were larger than 5 mm.[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]

Concerns with progestin only contraceptives

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 COC's, 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 dependent peristalsis and ciliary beat frequency.[69] The result of this interference is slowing of tubal transport, and mistiming of the arrival of the embryo into the endometrial cavity outside of the implantation window. Women on continuous progestin only contraceptives, with the

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[65] T. VAN DEN BOSCH, G. G. G. DONDERS, I. RIPHAGEN, P. DEBOIS, L. AMEYE,J. DE BRABANTER, S. VAN HUFFEL, D. VAN SCHOUBROECK and D. TIMMERMAN. Blackwell Science, Ltd Ultrasonographic features of the endometrium and the ovaries in women on etonogestrel implant. Ultrasound Obstet Gynecol 2002; 20: 377–380

[66] Petta CA, Faúndes A, Dunson TR, Ramos M, DeLucio M, Faúndes D, Bahamondes L. Timing of onset of contraceptive effectiveness in Depo-Provera users. II. Effects on ovarian function.Fertil Steril. 1998 Nov;70(5):817-20.

[67] Fotherby K, Howard G. Return of fertility in women discontinuing injectable contraceptives. J Obstet Gynaecol (Lahore). 1986 Apr;6 Suppl 2:S110-5.

[68] Bassol S, Garza-Flores J, Cravioto MC, Diaz-Sanchez V, Fotherby K, Lichtenberg R, Perez-Palacios G.Ovarian function following a single administration of depo-medroxyprogesterone acetate (DMPA) at different doses.Fertil Steril. 1984 Aug;42(2):216-22.

[69] Kugler P, Wrobel KH, Wallner HJ, Heinzmann U.[Histochemical and histological investigations on the human fallopian tube under different hormonal influences. I. Demonstration of ATPase with special reference to reactive ciliated cells] Arch Gynakol. 1976 Dec 10;221(4):345-66.

exception of depo-provera users[70], are at increased risk of ectopic pregnancy.[71] With the levonorgestrel implants (Norplant), the risk is 5 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 progesterone 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 does 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 endotheilal cells and the capillaries and the glandular and cellular components of the endometrium."*
>
> *"There may be changes in endometrial vascular constriction and dilatation 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*

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[70] Borgatta L, Murthy A, Chuang C, Beardsley L, Burnhill M. "Pregnancies diagnosed during Depo-Provera use" Contraception 66 (2002) 169–172

[71] Fylstra DL. Ectopic pregnancy not within the (distal) fallopian tube: Etiology, diagnosis and treatment. Am J. Obstet Gynecol. 2012 April p 289-299.© 2012 Mosby, Inc. All rights reserved.
doi: 10.1016/j.ajog.2011.10.857.

[72] Furlong LA Ectopic Prengnacy Risk When Contraception Fails.[FDA DATA] J Reprod Med Nov 2002; 47(11) 881-885.

[73] ACOG Practice Bulletin 121 July 2011 Long-Acting Reversible contraception: Implants and intrauterine devices

[74] Klipping C, Duijkers I, Remmers A, Faustmann T, Zurth C, Klein S, Schuett B. Ovulation-Inhibiting Effects of Dienogest in a Randomized, Dose-Controlled Pharmacodynamic Trial of Healthy Women Journal of Clinical Pharmacology, 2012;52:1704-1713

[75] Klipping C, Duijkers I, Remmers A, Faustmann T, Zurth C, Klein S, Schuett B. Ovulation-Inhibiting Effects of Dienogest in a Randomized, Dose-Controlled Pharmacodynamic Trial of Healthy Women Journal of Clinical Pharmacology, 2012;52:1704-1713

[76] T. VAN DEN BOSCH, G. G. G. DONDERS, I. RIPHAGEN, P. DEBOIS, L. AMEYE,J. DE BRABANTER, S. VAN HUFFEL, D. VAN SCHOUBROECK and D. TIMMERMAN. Blackwell Science, Ltd Ultrasonographic features of the endometrium and the ovaries in women on etonogestrel implant. Ultrasound Obstet Gynecol 2002; 20: 377–380

[77] EsHRE Capri Workshop Group Ovarian and endometrial function during hormonal contraception. Human Reprod [2001] 16 (7); 1527-1535

> *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 COC's.

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

[78] Donoghue JF, McGavigan CJ, Lederman FL, Cann LM, Fu L, et al. (2012) Dilated Thin-Walled Blood and Lymphatic Vessels in Human Endometrium: A Potential Role for VEGF-D in Progestin-Induced Break-Through Bleeding. PLoS ONE 7(2): e30916. doi:10.1371/journal.pone.0030916

[79] Fechner S, Husen B, Thole H, Schmidt M, Gashaw I, Kimming R, Winerhager E, Grummer R. Expression and regulation of estrogen-converting enzymes in ectopic human endometrial tissue Fertility and Sterility Vol. 88, Suppl 2, October 2007

[80] Creus M, Ordi J, Fabregues F, Casamitjana R, Carmona F, Cardes A, Vanrell J, Balash J. The effect of different hormone therapies on integrin expression and pinopode formation in the human endometrium: a controlled study. Human Reproduction Vol.18, No.4 pp. 683±693, 2003

[81] Rivera R, Yacobson I, Grimes D. The mechanism of action of hormonal contraceptives and intrauterine contraceptive devices. Am J Obstet Gynecol 1999; 181 (5) Part I 1263-1269.

[82] Krikun G, Booth C, Buchwalder L, Case, R, Rahman M, Schatz F, Buhimschi I, Lockwood C. Long-term progestin-only contraception in humans versus animal models. Ann. N.Y. Acad. Sci. 1221 (2011) 119–123 c 2011 New York Academy of Sciences.doi: 10.1111/j.1749-6632.2010.05930

[83] Bayle B The antinidatory activity of oral contraceptives Contracept Fertil Sex (Paris). 1994 Jun;22(6):391-5.

[84] Keller S.Progestin-only methods are very effective.Netw Res Triangle Park N C. 1995 Jun;15(4):4-8.

[85] Fechner S, Husen B, Thole H, Schmidt M, Gashaw I, Kimming R, Winerhager E, Grummer R. Expression and regulation of estrogen-converting enzymes in ectopic human endometrial tissue Fertility and Sterility

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[86] Klipping C, Duijkers I, Remmers A, Faustmann T, Zurth C, Klein S, Schuett B. Ovulation-Inhibiting Effects of Dienogest in a Randomized, Dose-Controlled Pharmacodynamic Trial of Healthy Women. Journal of Clinical Pharmacology, 2012;52:1704-1713

being able to achieve and sustain a positive pregnancy test, for several months after the long-term use of continuous progestin-only contraceptives.[87]

III. Copper and LNG-IUDs: potential for embryo formation and post ovulatory conditions

In discussing how IUD's 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 thus 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%.*"[88]

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 levonorgestrel at the level of the endometrium and thus has the additional actions of thickening of cervical mucus, and slowing of tubal motility.

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 1980's, 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, IUD's 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 IUD's 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*

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88 Glasier A, Baird D. Post Ovulatory Contraception in Bailliere's Clinical Obstetrics and Gynaecology Vol 4 No 2 June 1990 Copyright Bailliere Tindall. ISBN 0-7020-1477-X

> *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."*[89]
> *"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*."[90]

However, the use of IUD's 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 1997review article which states:

> "*The prevention of pregnancy before implantation is contraception and not abortion*."[91]

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."*[92]
>
> *"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*."[93]

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[89] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[90] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[91] Glasier A, Emergency Postcoital Contraception (Review) New England J of Med 1997; 337 (15) 1058-1064.
[92] Barbarosa IC, Oddvar B, Olsson SE, Odling V, Johansson E, Ovarian function during use of levonorgestrel releasing IUD. Contraception 1990; 42-51.
[93] Barbosa I, Olsson SE, Odling V, Goncalves T and Coutinho E. Ovarian function after seven years use of a levonorgestrel IUD. Advances in Contraception, 1995; 11: 85-95. Kluwer Academic Publishers. Netherlands.

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[94] on "emergency contraception" describes the use of IUD's for EC:

> "*Copper□bearing IUDs*
> *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 IUD's 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) IUD's do not prevent ovulation. Women release eggs only a little less often than normal, even on the LNG IUD. [95] [96] [97] [98]
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.[99]
3) Although IUD's can decrease the absolute number of sperm which reach the fallopian tubes, [100] still sperm are capable of reaching the fallopian tube in Copper IUD and LNG IUD's, and have been directly observed and recovered from the tubes of women using IUD's.[101] [102] [103]

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[94] Trussell J. Raymond EG. " Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy" available at http://ec.princeton.edu/questions/ec-review.pdf [last visited 5 26 2013].
[95] Ortiz ME, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological basis of their mechanism of action. Contraception 75 (2007) S16–S30.
[96] Glasier A, Emergency Postcoital Contraception (Review) New England J of Med 1997; 337 (15) 1058-1064
[97] Barbosa I, Olsson SE, Odling V, Goncalves T and Coutinho E. Ovarian function after seven years use of a levonorgestrel IUD. Advances in Contraception, 1995; 11: 85-95. Kluwer Academic Publishers. Netherlands.
[98] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[99] Barbosa I, Olsson SE, Odling V, Goncalves T and Coutinho E. Ovarian function after seven years use of a levonorgestrel IUD. Advances in Contraception, 1995; 11: 85-95. Kluwer Academic Publishers. Netherlands.
[100] Ortiz ME, Croxatto HB. Copper-T intrauterine device and levonorgestrel intrauterine system: biological basis of their mechanism of action. Contraception 75 (2007) S16–S30.
[101] Barbosa I, Olsson SE, Odling V, Goncalves T and Coutinho E. Ovarian function after seven years use of a levonorgestrel IUD. Advances in Contraception, 1995; 11: 85-95. Kluwer Academic Publishers. Netherlands.

4) Fertilizations do take place in IUD users. Embryos have been directly recovered from the fallopian tubes of IUD users. [104] [105] In addition, the documented pregnancy rate of .1% proves that embryos can be created during the use of the IUD.
5) Embryos created during the use of the Copper T IUD's develop abnormally either due to toxic effects of the copper on sperm, or toxic effects on the egg, or direct toxicity to the embryo.[106] [107] [108] [109]
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 IUD's and Progestin IUD's.[110] [111] [112] [113] [114] [115] [116] [117] [118]

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[102] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[103] Ortiz ME, Croxatto HB Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception 75 (2007) S16–S30
[104] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[105] Ortiz ME, Croxatto HB Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception 75 (2007) S16–S30
[106] ESHRE Capri Workshop Group Intrauterine Devices and intrauterine systems. Human Reproduction Update, Vol.14, No.3 pp. 197–208, 2008
[107] Ortiz ME, Croxatto HB Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception 75 (2007) S16–S30
[108] Ortiz ME, Croxatto HB, Bardin CW. Mechanisms of action of intrauterine devices. Obstet Gynecol Surv. 1996 Dec;51(12 Suppl):S42-51.
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Potential Role for VEGF-D in Progestin-Induced Break-Through Bleeding. PLoS ONE 7(2): e30916. doi:10.1371/journal.pone.0030916
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[113] Glasier A, Emergency Postcoital Contraception (Review) New England J of Med 1997; 337 (15) 1058-1064.
[114] Guney M, Oral B, Karahan N, Mungan T Expression of Leukaemia inhibitory factor (LIF) during the windo wo implantation in copper T380A Intrauterine device users European J of Reprod Health Care Sept 2007; 12(3):212-219.
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[117] Ortiz ME, Croxatto HB Copper-T intrauterine device and levonorgestrel intrauterine system: biological bases of their mechanism of action. Contraception 75 (2007) S16–S30.
[118] Stanford JB, Mikolajczyk RT. Mechanisms of action of intrauterine devices: Update and estimation of postfertilization effects. Am J Obstet Gynecol. 2002 Vol 187(6) 1699-1708.

7) Pregnancies diagnosed during the use of the IUD are usually in the fallopian tubes [ectopic pregnancies][119] [120] [121], giving evidence that the embryos which survive to enter the uterus are selectively "lost".[122]
8) IUD's 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.[123] IUD's 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, IUD's clearly can cause the death of embryos both before and after implantation, and this is likely their major mechanism of action.

IV. Emergency contraceptives (Plan B and Ella): potential for embryo formation and post ovulatory conditions

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 agonists have variable mechanisms depending on the timing of administration in relationship to the LH surge and ovulation.

A. 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 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.[124] [125] [126] 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. [127] [128] [129]

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[119] Bouyer J, Coste J, Fernandez H, Pouly JL, Job-Spira N. Sittes of ectopic pregnancy: A 10 year population-based study of 1800 cases. Human Reproduction Vol.17, No.12 pp. 3224–3230, 2002.
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[123] Glasier A, Baird D Post Ovulatory Contraception in Bailliere's Clinical Obstetrics and Gynaecology Vol 4 No 2 June 1990 Copyright Bailliere Tindall. ISBN 0-7020-1477-X
[124] Gemzell-Danielsson K, Mechanism of action of emergency contraception. Contraception 82 (2010) 404–409

B. 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.[130] [131] [132] [133] 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. [134] [135] [136] [137] [138] [139]

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. [140] 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 induces regression of the corpus luteum in about 50 percent of women*."[141]

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[127] Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. Contraception 2001; 63:123-129.
[128] Gemzell-Danielsson K, Mechanism of action of emergency contraception. Contraception 82 (2010) 404–409
[129] Croxatto HG, Brache V, Pavez M, Cochon L, Forcelledo MI, Alvarez F, Massai R, Faundes A, Salvatierra AM Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75 mg dose given on the days preceding ovulation. Contraception 70 (2004) 442– 450.
[130] Gemzell-Danielsson K, Mechanism of action of emergency contraception. Contraception 82 (2010) 404–409
[131] Hapangama D, Glasier AF, Baird DT. The effects of peri-ovulatory administration of levonorgestrel on the menstrual cycle. Contraception 2001; 63:123-129.
[132] Croxatto HG, Brache V, Pavez M, Cochon L, Forcelledo MI, Alvarez F, Massai R, Faundes A, Salvatierra AM Pituitary-ovarian function following the standard levonorgestrel emergency contraceptive dose or a single 0.75 mg dose given on the days preceding ovulation. Contraception 70 (2004) 442– 450.
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[141] Glasier A, Emergency Postcoital Contraception (Review) New England J of Med 1997; 337 (15) 1058-1064.

C. 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 prevents fertilization. In fact, the evidence shows that neither high dose progestins[142] [143] [144] [145] [146] nor progesterone blockers[147] [148] 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…."[149]

D. 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.[150]

Ella, causes a significant effect on tubal function, blocking progesterone receptors in the tube[151], 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.[152] [153]

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[152] Christow A, Sun X, Gemzell-Danielsson K. Effect of mifepristone and levonorgestrel on expression of steroid receptors in the human Fallopian tube. "Molecular Human Reproduction 2002; 8 (4);333-340

[153] Glasier A, Baird D Post Ovulatory Contraception in Bailliere's Clinical Obstetrics and Gynaecology Vol 4 No 2 June 1990 Copyright Bailliere Tindall. ISBN 0-7020-1477-X

E. 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. [154] [155]

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.[156] [157] [158] [159] [160]

F. Effect of high dose progestin (Plan B) or Progesterone blockers (Ella and RU-486) 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

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[158] Lalitkumar PBL, Lallitkumar S, Meng CX, Stavreus-Evers A, Hambiliki F, Bentin-Ley U, Gemzell-Danielsson K, Mifepristone, but not levonorgestrel, inhibits human blastocyst attachment to an in vitro endometrial three-dimensional cell culture model Human Reproduction pp. 1–7, 2007.

[159] Marions L and Gemzell Danielsson K. Expression of cyclo-oxygenase in human endometrium during the implantation period. Molecualr Human Reproduction 1999; 5(10); 961-965 .

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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 RU-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[161]

A review article on Ella [162] for pharmacists states:

> *"The mechanism of action of ulipristal in human ovarian and endometrial tissue is identical to that of its parent compound mifepristone.[163], [164]. 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.[165] However, only limited safety and reproductive toxicology studies have been performed with ulipristal, despite International Conference on Harmonization Good Clinical Practice (ICHGCP) requirements.[166] Nevertheless, the results from 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 loss of 4 of 5 fetuses.[167]*

[161] European Medicines Agency, Product Information Annex I (19/03/2010 Ellaone-H-C-1027-IA-04) (updated May 7, 2010): sec. 5.3, p2. www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001027/WC500023670.pdf (accessed 2010 Sept 25).
[162] Harrison DJ, Mitroika JG. "Defining Reality: the The Potential Role of Pharmacists in Assessing the Impact of Progesterone Receptor Modulators and Misoprostol in Reproductive Health". Ann Pharmacother. 2011 Jan;45(1):115-9. doi: 10.1345/aph.1P608. Epub 2010 Dec 21.
[163] Attardi B, Burgenson J, Hild S, Reel J. In vitro antiprogestational/antiglucocorticoid activity and progestin and glucocorticoid receptor binding of the putative metabolites and synthetic derivatives of CDB-2914, CDB-4124, and mifepristone. J Steroid Biochem Mol Biol 2004;88:277-88.
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> *Table 1 shows the effects of single oral doses of ulipristal on early pregnancy in rats[168] and Macaque monkeys.[169] 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[170] continues:

> "*Further experience with abortion in humans is supplied by the 2 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.[171] And in the second, 4 of 6 women "miscarried", and the remaining 2 were lost to follow-up.[172] 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.

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[168] Teutsch G, Philibert D. History and perspectives of antiprogestins from the chemist's point of view. Hum Reprod 1994;9(suppl 1):12-31.

[169] Tarantal AF, Hendrickx AG, Matlin SA, et. al. Effects of two antiprogestins on early pregnancy in the long-tailed macaque (Macaca fascicularis). Contraception 1996;54:107-15.

[170] Harrison DJ, Mitroika JG. "Defining Reality: The Potential Role of Pharmacists in Assessing the Impact of Progesterone Receptor Modulators and Misoprostol in Reproductive Health". Ann Pharmacother. 2011 Jan;45(1):115-9. doi: 10.1345/aph.1P608. Epub 2010 Dec 21.

[171] Fine PT, Mathe H, Ginde S, Cullins V, Morfesis J. Ulipristal acetate taken 48-120 hours after intercourse for emergency contraception. Obstet Gynecol 2010;115(2 Pt 1):257-63.

[172] Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. Lancet 2010 375:555-62. DOI 10.1016/S0140-6736(10)60101-8

V. Summary and Conclusions

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.