Morning After Pills/Emergency Contraception: Fact, Fiction & Fraud

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Abstract: Morning After Pill (MAPs or "Emergency Contraception") formulations and the research regarding their efficacy and mode of action have evolved significantly over the past two decades. Much of what is commonly known or assumed about EC is not based in actual knowledge of the available research, or is simply not supported in the research literature. This paper examines what is known and unknown about EC, particularly with regard to an abortifacient effect, debunks myths and false assumptions, and calls for prolife medical experts to apply critical analysis to the present fact base on EC.

Summary of Conclusions

- The current realm of published literature, public information (including media coverage), and public policy regarding EC is a disconcerting jumble of fact, fiction, and fraud.

- The course of "research" that led to current EC formulations and protocols was unethical and scientifically illegitimate.

- The reported "effectiveness" of EC in preventing pregnancy is at best, vastly overstated (due to faulty analytical models) and at worst, is scientifically indefensible given the regimens' modes of action for fertility disruption.

- While touted as a major mode of action, EC appears to prevent (or delay) ovulation only when given within a small window of the fertile cycle - 2 to 7 days before ovulation would have naturally occurred. EC given any closer than 2 days of ovulation has no effect on preventing ovulation.

- Given the narrow window of effectiveness EC does have, indiscriminately providing it to all women who seek it, without screening them for their fertility cycle stage, is poor medical practice and a massive consumer fraud. Making EC available over the counter for self-administration is even more scandalous.

- Claims that EC prevents the implantation of a conceived child (an abortifacient effect) are entirely unsubstantiated within the animal model research, and there is not sufficient evidence within human tests to presume or conclude that the effect occurs, or is even likely.

- Some of the research points to a potential abortifacient effect not from failed implantation, but possibly luteal phase dysfunction or bleeding/early menstrual episodes. The evidence and physiological modeling for this potential effect may be more credible than an anti-implantation effect.

- Prolife scientists and medical professionals must step forward to provide a critical analysis of the existing scientific literature to determine the validity of the conclusions made therein and provide clarity regarding the abortifacient effect.

- Numerous concerns regarding the validity of EC as a medical/social panacea remain relevant-namely, long-term health risks to women, increased exposure to STD risk, and promotion of promiscuity and exploitation of teens and young women by 'predatory' males.

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Introduction

For decades now, researchers, pharmaceutical companies, and family planning and population control advocates have explored and promoted the idea that a medication could be, and should be, devised to prevent pregnancy from occurring after intercourse has occurred - a 'magic pill' that could be taken the morning after sex to prevent an unwanted pregnancy. Hence, the "morning after pill" (MAP) and its medical title "emergency contraception" (EC) has become part of our lexicon.

Inherent in the logic of using a drug after intercourse where sperm are present to fertilize a potentially present ovum, prolife advocates have instinctively and rightly questioned whether such a drug would have the effect of causing an abortion by preventing implantation into the uterus. This effect is properly called "abortifacient." This concern is particularly poignant in light of the information available about the impact the regular use of hormonal birth control, such as oral contraception (OC) and other hormonal methods, have on the endometrium. It has long been recognized that OC disrupts the normal fertile development of the endometrium, thereby making it less receptive to or, perhaps, resistant to the implantation of an embryonic child. The potential abortifacient effect of the "hostile" endometrium has been both a point of concern and disagreement within the prolife community.

In the case of both OC and EC, there is ***suggestive*** evidence on the abortifacient effect. Still, there is no ***definitive*** evidence on the abortifacient effect of both these hormonal drug regimens. This paper reviews, and takes a critical look at, the existing scientific literature on EC and how they work. This analysis will review and examine the claimed effectiveness of EC, as well as what is known about the abortifacient effect of EC, and it will also outline those areas needing critical scientific review by the prolife movement to draw conclusions about the abortifacient effect. Importantly, this analysis challenges assumptions, exposes ethical concerns, examines physiological modeling, and questions motives regarding the research and promotion of EC.

The focus of this research is exclusively on the abortifacient effect of EC and its overall presumed effectiveness. There are other serious medical, social, and moral considerations that this paper does not discuss regarding the validity of EC as a form of "medical care." The long-term health risks of repeated high doses of hormones is unknown. Subjecting women's long-term health to unknown risks for a "treatment" that has marginal effectiveness raises significant ethical questions. Likewise, women who abandon other contraceptive practices, particularly condom use, increase their risk of unintended pregnancy and risk of exposure to sexually transmitted diseases.

The ready availability of EC can promote cavalier, promiscuous attitudes toward sexual activity and responsibility. In addition, EC creates a manipulative, even exploitive, tool for men to utilize in seducing women into sexual activity. This is a particularly grave problem in light of the disturbing data on adult men preying on minor girls in sexual relationships. All of these issues are of serious consequence and ought not be dismissed in the general social and political debate regarding EC.

Readers will find this presentation challenges two primary assumptions (nearly dogmas) regarding EC. First is the assumption by EC proponents that EC is highly effective. Second is the assumption by prolife advocates that EC is abortifacient. Unless and until one has reviewed at a minimum the studies

reviewed here, acceptance and promotion of either of these assumptions is not factually warranted. The primary conclusion of this work is that logical and critical analysis must be applied now to the available research, while political and public relations activities take a back seat.

Researcher Disclaimer/Disclosure: In the spirit of full disclosure, I offer the following on my perspectives and background: As a prolife activist and a Catholic, I am opposed to any drug or device that causes an abortion or interferes with conception/pregnancy. I am a certified instructor in the Sympto-Thermal method of natural family planning, and have taught, along with my wife, hundreds of people how to use the method. My academic training includes a master's degree in policy analysis and evaluation (including logic and statistical analysis). Except for my training in natural family planning, I have no medical education or background. All information and comments contained herein are the product of the author and do not reflect any official position or statement of my employer, Right to Life of Michigan.

Physiology, Biochemistry, and EC History

It is critically important to the EC-abortifacient debate to have a solid understanding of the basic physiology of human reproduction. The interplay of the reproductive hormones with the reproductive organs is a complex, sequential, and masterfully balanced orchestration. Disruption of a particular element of this balance will have predictable outcomes later in the sequence. Like falling dominoes, the appearance of one triggering mechanism prompts a response from another fertility element, whether that be organ or hormone.

The essential fertile features of a woman's monthly cycle begin with hormonal signals which are produced by the pituitary gland at the base of the brain. The pituitary first releases the Follicle Stimulating Hormone (FSH), which prompts one follicle (egg-containing structure) within the ovaries to begin to mature. This follicle is called the "dominant" or "leading" follicle. One result of the follicle maturing is the production of the hormone estrogen.

Estrogen has several effects: it causes the endometrium to develop, becoming enriched with blood and other biochemical receptors, preparing it to receive a conceived embryo; it causes the development of mucus which is necessary for the transport of sperm for fertilization to occur; it also signals the pituitary to release another hormone called "Luteinizing Hormone" (LH). The surge in LH prompts the expanding follicle to rupture and release the ovum (ovulation), which from there begins its journey into and through the Fallopian tube. As will become apparent, the surge in LH prompting follicle rupture is a critical element in EC effectiveness.

After ovulation, the empty follicle is given a new name, the corpus luteum, and takes on the function of producing the hormone progesterone. Progesterone has two key functions: it signals the pituitary that ovulation has occurred, shutting off further LH release, and it helps sustain the fertile condition of the endometrium. If no pregnancy occurs, the corpus luteum will cease to function after about two weeks, the endometrium will begin to breakdown, and menstruation will

begin. If an embryo does implant in the uterus, it sends a hormone the corpus luteum to keep functioning, and the pregnancy will be sustained until the placenta forms and produces its own progesterone. The period of time in the fertile cycle from ovulation until menstruation is known as the "luteal phase," as it is under the influence of corpus luteum.

If sperm are present within the 12 to 24 hours when the released ovum is viable, and fertilization occurs, it will take 6 to 9 days for the developing embryo to travel through the Fallopian tube to the uterus and implant in the endometrium. In some cases, the embryo does not reach the uterus and instead implants in the wall of the Fallopian tube. This is known as an ectopic or "tubal" pregnancy. This child and pregnancy are not viable. If not surgically removed, the tube will rupture and threaten the mother's life.

Of particular importance is the physiology of the endometrium and what makes it receptive or hostile to implantation of an embryo. Much of the understanding of this physiology comes from the field of infertility treatment. Medical researchers have endeavored to understand why some women have difficulty achieving or maintaining a pregnancy. Thus, detailed research has identified the cellular structures, hormonal condition, and even specific chemical molecules that appear to be important to endometrial receptivity. While there is much research and writing which speculates on the endometrial effects of EC, in reality there is a very limited amount of research that directly examines the effect of EC on these endometrial factors.

With regard to the historical development of post-coital contraceptive treatments, researchers initially focused on either using various doses of the hormones used in OC to attempt to prevent ovulation, if it had not occurred by the time of treatment, or creating a hostile endometrium to prevent the embryo from implanting. It should be noted that abortion advocates have redefined the beginning of "pregnancy" as the point of implantation, rather than at conception, thereby trying to sidestep the entire abortifacient issue. The true and historical definition of pregnancy, however, begins at conception.

The first EC regimen to have gained recognition for effectiveness has become known as the "Yuzpe regimen," named after the researcher-physician who pioneered it. The Yuzpe regimen consists of the patient taking a dose of 100 mg ethinyl estradiol (EE) and 1 mg of norgestrel (or 0.5 mg of levonorgestrel (LNG), and repeating the same dosage 12 hours later. This estrogen-progesterone combination is essentially a quadruple dose of a typical combined oral contraceptive ("regular birth control"). The regimen is recommended to be taken within 72 hours (3 days) of intercourse. Though researchers were initially upbeat about the presumed effectiveness of this regimen for preventing pregnancy (less than 4% of women taking it became pregnant), many women had severe nausea and vomiting as a side effect, prompting researchers to look for a better option.[1, 2]

Researchers then turned their attention more toward the progesterone side of the regimen, testing the effect of two doses of 0.75 mg of levonorgestrel (LNG), 12 hours apart. Results with LNG showed similar pregnancy rates, but greatly reduced side effects, making it a more acceptable option. This regimen of LNG is now being marketed under the brand name "Plan B."

Lastly, researchers have tested the abortion pill RU-486 (mifepristone) as EC. There has been a general presumption on the part of prolife and pro-abortion advocates that RU-486 would be presumed to have an abortifacient effect. **Unlike the more ambiguous study results on endometrial receptivity using the Yuzpe regimen or Plan B, the hostile effects to the endometrium caused by use of RU-486 are quite apparent. Somewhat surprisingly, however, studies show that RU-486 has been found to effectively disrupt ovulation, if taken prior to the LH surge; therefore, its effects are not entirely or always abortifacient.** [3, 4]

PART I: EC Effectiveness: How Well Does it Really Work?

In most scientific studies, the way to determine if a treatment is effective is to treat some of the patients with the drug in question, while giving an equal group of patients (a control group) a placebo. In the vast majority of studies done on EC, the women taking the regimen were actual patients who were looking to prevent a pregnancy. Because it would be unethical to have a control group receiving a placebo, all of the conclusions on the effectiveness of EC in preventing pregnancy had to be estimated ***indirectly*** by measuring actual pregnancies which occurred against statistically ***estimated*** pregnancies given the group size in the study. Various early studies had shown effectiveness rates from as low 57% to as high as 85%, with the bulk of the studies showing rates in the 70th and 80th percentiles.[5]

What is very apparent when reviewing the expected pregnancy rates, and what the literature has been gradually revealing over time, is **the original expected pregnancy rates have been unreliable and overstated, thus overstating the effectiveness of EC.** [6, 7, 8] In developing the first statistical formulas for estimating expected pregnancies, researchers oversimplified the nature of the fertility cycle and built their numbers upon these faulty assumptions. A serial examination of the formulas researchers have developed to estimate conception/pregnancy rates shows that minor independent errors in one formula are then assumed into the next formula, which compounds with an independent error in that study, and so on, thereby pushing the estimates further and further from being accurate.

Faulty Foundation - Assumptions that distort the formula

The most recognized and frequently utilized conception probability formula was developed by Dixon, et al., in 1980. [9] Using data from studies on the probability of achieving pregnancy from intercourse on a given day of a cycle, Dixon created a probability table for the likelihood of pregnancy on any given day in the cycle. Dixon used three studies that tracked conception rates for couples attempting to get pregnant.[10, 11, 12] These studies tracked the dates of intercourse in relation to the presumed or identified date of ovulation in the cycle and the number of pregnancies which resulted.

Dixon synthesized the data to create a probability factor for a pregnancy resulting from a single incident of intercourse, based on the timing of intercourse in proximity to the fertile window. Previous research has conclusively shown that conception can occur up to 24 hours after

ovulation, and that sperm deposited by intercourse up to five days prior to ovulation can survive in the woman's reproductive tract to fertilize successfully the ovum after ovulation occurs. Thus, most researchers work from the conclusion that the fertile window includes the day of ovulation plus the five days prior to ovulation.

Over time, however, subsequent research has raised some serious questions about the validity of Dixon's probability table and expected pregnancy rates. To create his probability table, Dixon takes the determined probability of pregnancy for a given day within the 6-day fertile window from the three studies, then includes an arbitrary "weighted average" factor to compensate for the fact that he is only estimating the date of ovulation, and finally averages it all together. There is no theoretical model or rationale given for the arbitrary coefficients that Dixon applies to the probabilities for the estimated day of ovulation. In essence, it is a mathematical "fudge factor" without any empirical basis or biological model.

Again, this arbitrary factor is applied to the probabilities from the three studies on pregnancy probabilities. The first study by Barrett and Marshall involved married couples who were attempting to get pregnant. The couples were experienced in using basal body temperatures to monitor fertility.[10] The second study, by Schwartz, et. al., examined pregnancy rates for women receiving a single, clinical artificial insemination from donors due to the infertility of their husbands.[11] A third study by Vollman monitored 74 married women, who already had given birth at least once and who were also experienced with monitoring basal body temperatures.[12] For both empirical and logical reasons, the pregnancy probabilities for these studies overstate the typical probabilities for pregnancy in the general public.

In the Schwartz study, the artificial insemination was intracervical, meaning all the sperm were deposited beyond the cervix in the uterus. In normal intercourse, sperm are deposited into the vagina and must travel through the cervix. Significant numbers of the sperm do not pass through the cervix. Thus, in the Schwartz instance, exposure to sperm is significantly higher, presenting in theory a higher probability of pregnancy. In the Vollman study, all the subjects were mothers, meaning they had proven fertility and thus would have an higher than average rate of fecundity. Even if these above average fertility/pregnancy factors raised the calculated probabilities only slightly, they still skew the model toward a probability that is too high. Combined with the arbitrary weighting factor, there is good reason to question the accuracy of Dixon's probability table.

So beginning with a probability table that overestimates potential pregnancy, Dixon then applies those probabilities to the women in the study who came in to receive a dose of emergency contraception. To determine how many of these women would be expected to become pregnant, Dixon estimated each woman's day of ovulation (and fertile window), then multiplied the number of women identified for each day of the fertile cycle times the probability of pregnancy from a single instance of intercourse on that day. Here is where Dixon, and most early research on the effectiveness of EC, goes significantly off track.

To establish the subjects' stage of the menstrual cycle, Dixon took the date each woman noted as

the start of her present menstrual cycle, then projected when the next menstrual cycle would begin based on the subject's stated "regular" cycle length. From that projected day of next menses, 14 days is subtracted to determine the day of ovulation. [Author's note: For anyone experienced in fertility awareness, this method of calculation for estimated day of ovulation is hard to be taken seriously.]

Rare indeed is the woman whose cycles are the same number of days each "month." For any given woman, cycle length variation of 1 to 7 days is considered to be within the range of normal fertility. One study of over 650 women with "regular" cycles, with a median length of 28 days, found only 12.4% of the cycles were actually 28 days in length.[13] Looked at another way, it is possible that when Dixon starts with the identified first day of the current cycle, and then adds the assumed "regular" number of days to determine the start of the next cycle, calculation is likely to be in error by one day or more **up to 87.6%** of the time -- **87.6%!**

Dixon assumes every women will have a cycle of a predictable length and that they know exactly what day the study cycle began. A small study by Stirling and Glasier found that only 48% of women presenting for EC were "absolutely certain" the dates their cycle started. Another 23% could identify the start date within plus or minus 1 day, while 13% could estimate only within plus or minus 3 days. The remaining 16% could only estimate the start of their cycle within a week or more.[7]

Next, Dixon assumes every woman has a 14-day luteal phase (from ovulation to start of next menses). While the luteal phase is more consistent and predictable for any given woman (usually a 1-2 day variation in length), it is reasonable to assume that any fixed average day estimate (14 days) will be off by 1 to 2 days up to 50% of the time. In addition, some women may never have a 14-day luteal phase (their range may be 11 to 13 days). For such women, Dixon's calculations would be substantially off ***every*** time.

There is a saving grace to all of these variations which may make Dixon's estimates somewhat salvageable - that being the law of averages among all this variation. A woman may be off by 1 or 2 or more days in identifying the day her cycle began. But her cycle length is likely to vary by 1 or more days as well. The time of her ovulation and length of luteal phase will vary. So while any one factor may be off by a day or two, the other possible variations could "correct" *for* it in the opposite direction, making Dixon's estimates not nearly so inaccurate.

However, there are still more factors that could compound the error in overestimating EC effectiveness. Dixon's study, and almost all the others, purposely screened out women with any type of medical complications and all those with "irregular" cycles. Thus, suggesting that the use of EC will prevent 70% of women "expected" to get pregnant from unprotected intercourse from actually getting pregnant overestimates the effect it will have on women with irregular cycles and infertility issues.

Another factor is the natural infertility rate of both the women and the men involved in seeking EC. The probability tables from the original three pregnancy studies, compounded and averaged

by Dixon, were based on couples with proven fertility or no known infertility problems. It is a commonly known fact that infertility rates have been increasing over the past few decades. Still another variable is that some women seeking EC do so because of a condom "failure." In these cases, it is difficult to determine the extent of sperm exposure the woman may have experienced. Their probability of pregnancy would certainly not be equivalent to those of the women in the studies used to determine Dixon's probability rates.

Beginning the Correction

Some of the research done with regard to EC efficacy and pregnancy probabilities in the 20-plus years since Dixon's probability table was published has shown that the original effectiveness claims are likely to be very unreliable. In 2000, Wilcox, et. al. published a study that captured and quantified the variations in cycles discussed above (and known empirically by those experienced in natural fertility awareness).Wilcox notes that current clinical guidelines assume a 14-day luteal phase, with several days before ovulation, and a day or two afterward making up a woman's monthly fertile window. After a careful hormonal analysis of the cycles of women seeking pregnancy and considered to have "regular" cycles, Wilcox makes the following statements and conclusions:

> "It follows that in the usual menstrual cycle lasting 28 days, the fertile days would fall between days 10 and 17. The assumptions, however, are outdated. First, only a small percentage of women ovulate exactly 14 days before the onset of menses. This is true even for women whose cycles are usually 28 days long. Among the 69 cycles for 28 days in our study, ovulation occurred 14 days before the next menses only 10%. Time from ovulation to next menses ranged from 7 to 19 days (days 10 to 22 of the menstrual cycle). Thus, the fertile window can occur much earlier or later in the cycle than clinical guidelines suggest."[14]

Wilcox and colleagues took the next logical step a year later (2001) and published a study re-examining Dixon's pregnancy probability table.[15] Whereas as Dixon created probabilities of pregnancy relative to the assumed day of ovulation, Wilcox created probabilities based on the given day of the cycle from the start of menses. This was partly as a result of the previous work which recognized that the fertile window has a much broader distribution within the cycle. Wilcox then applied Dixon's probabilities to his current data, but this time assuming a 13-day, rather than a 14-day luteal phase, claiming it to be a more accurate number without explanation. The comparison found that while the two probability tables did parallel each other, during the highest days of fertility (days 13-19 of the cycle) Dixon's estimates were all higher, ***up to 50% higher***, around the peak fertile days.

Wilcox notes that these probability differences would alter effectiveness rates very little if women sought EC during the entire time of their cycle. But on the presumption that women are more likely to seek EC when they have had intercourse the middle/fertile time of their cycle, Wilcox concludes, "...Dixon's approach would produce inflated estimates of the expected pregnancy rate, and overestimate the efficacy of post-coital contraception." Finally, Wilcox notes that two studies published in 1998 using his 1995 pregnancy probabilities did not take into

account the cycle variance he quantified in 2000. Thus, those studies' calculations "could lead to overestimation of the efficacy of the treatment."[15]

James Trussell is another researcher who has been the lead author of several studies on EC efficacy, and who worked in collaboration with Wilcox to develop the 2001 revised pregnancy probabilities. In 2003, Trussell took these new probabilities and applied them to the data of two previous studies (Population Council and WHO) which used the Dixon method. As a result, the effectiveness estimates for these studies were meaningfully reduced as noted in Table 1.[16]

Table 1

	Population Council		WHO	
	Dixon	Wilcox/Trussell	Dixon	Wilcox/Trussell
Overall expected pregnancy rate	6.2%	==> 5.4%	7.4%	==> 5.2%
Typical user effectiveness	59.3%	==> 53.0%	62.5%	==> 48.8%
Perfect user effectiveness	66.9%	==> 66.0%	61.9%	==> 51.4%

These downward revisions begin to capture the reality that early estimates on EC efficacy were significantly overstated, especially with early estimates claiming up to 85% effectiveness. Trussell concludes that the expected pregnancy estimates under the "old method" are too high and thus the effectiveness rate is too high as well. The pregnancy estimates are "too high" because the "old method" assumptions are less reliable and the pregnancy probabilities are based on women with proven fertility or without known fertility problems.

As Trussell states, "conception probabilities employed in this paper might be expected to be too high because women were included in the North Carolina study only if they had no known infertility problems, and the conception probabilities are estimated only among ovulatory cycles."[16] In the general population, a certain percentage of women presenting for EC will actually be experiencing an annovulatory cycle. Metcalf and MacKenzie found rates of 9% to 38% of women may not ovulate during a given cycle.[17]

In 1992, Glasier et. al., compared the Yuzpe regimen against RU-486, with EC effectiveness determined using the standard calculations by estimated day of the cycle. But the study also did biochemical analysis later to cross-check the estimated cycle day with the biochemical evidence of ovulation. The cross-check found that 51% of the women calculated to be in the luteal phase at the time of treatment had actually **not yet** ovulated (187 of 368). Additionally, 21% of the

women assumed to be pre-ovulatory had **already** ovulated. (44 of 205). Hence, the statistically-based calculations for effectiveness were based on **28.9%** of the women being misclassified (231 of 800).[3]

It should be noted that in this study, misclassifying 51% of the women thought to be post-ovulatory, when they were in fact, pre-ovulatory, would argue for a higher overall effectiveness of the EC, even after subtracting the 21% of those thought to be pre-ovulatory and who were actually in the luteal phase. But it also means that these women cannot automatically be counted as subject only to a post-conception abortifacient effect, as their misclassification would suggest.

In the above study, 28.9% of the women were misclassified on the opposite side of their presumed day of ovulation. This gives a broad picture about the inaccuracy of estimating stage of cycle with respect to ovulation. However, true probabilities for pregnancy lie in the 6-day fertile window. Classifying which women are in that actual window at the time of treatment would offer a real examination of EC effectiveness. If nearly 30% of women can be misclassified regarding ovulation, then classifications which presume women to be in their fertile window are equally subject to error, perhaps more so since ovulation is a single, identifiable event, while determining the fertile window is more subjective.

A group of Spanish researchers (Espinos, et.al., 2001) sought to quantify how often women seeking EC were actually in their fertile window and how accurately Trussell's model estimated the expected number of pregnancies. They collected information from the women on when their current menstrual cycle began and the normal length of their cycle, as Trussell and others had done. In addition, blood samples were drawn in order to test hormone levels and determine at what stage in their cycle the subjects actually were. Using Trussell's model, 119 women were calculated to be within a 7-day fertile window of -5 days to +1 day of ovulation. Of the 119, 20 were at ovulation day +1, which most researchers believe is a very marginally fertile day at best. Thus, the Trussell method calculated 99 women to be in their 6-day fertile window.

By explicit chemical analysis, however, Espinos found 51 women instead of 119 to be in the 7-day fertile window, and only 47 rather than 99 in the 6-day window. **In essence, the statistical method of calculation overstated the number of women in their fertile window by 100%**. This result left Espinos to conclude, "The calculation of the ovulation period from menstruation is, thus, highly inaccurate even in women with regular cycles."[6]

In 2003, Severi, et. al., conducted a study similar to Espinos, using transvaginal ultrasound to determine the cycle day of 163 women seeking EC (Yuzpe regimen).Using the standard cycle day calculations (Dixon), the study placed 64 women in the pre-ovulation or ovulation day category, and 99 women as post-ovulatory. After doing the ultrasonography, Severi classified 96 as either pre-ovulatory or at day of ovulation, and 67 as post-ovulatory. With the Dixon method, 50 women were calculated to be in the 6-day fertile window, but Severi found 74 actually in that window, **a 50% difference**. (See Table 2)

Table 2 - Cycle Dating
Calendar Calculation v. Transvaginal Ultrasonography

	Pre-ovulatory	Post-ovulatory	Fertile Window
Dixon	64	99	50
Severi	96	67	74

These researchers concluded, "Because the probability of conception changes according to the different days of the menstrual cycle, calculation of the conception risk on the basis of the hypothetical day of ovulation becomes very unreliable. As a case in point, more than 70% of our sample reported regular cycles, but transvaginal ultrasonography revealed that at least one third of these women had a discrepancy of more than 48 hours."[8]

One interesting note about the Severi - there were 7 observed pregnancies among the 163 women seeking treatment. This is a rate of 4.2%. According to the Dixon calculations, in the absence of treatment, there was an expected 7.6 pregnancies. With the revised ultrasonography estimates, there were 11.3 pregnancies expected. Thus, if this had been a study on EC effectiveness using the Dixon method, the conclusion would have been that the EC was **0% effective.** (i.e. observed pregnancies matched expected pregnancies).Why the authors did not comment on this is puzzling at best and suspicious at worst.

Also interesting to note is that historically, the estimated expected pregnancy rate for any given random act of intercourse has ranged from 2% to 5%.[18] Severi's study found a 4.2% pregnancy rate among women being treated with EC. This is right in the expected range for women using nothing at all. Again, no comment from the authors. Similarly, von Hertzen and Van Look found a 3.2% pregnancy rate among Yuzpe regimen users, but only 1.1% among LNG (Plan B) users.[2] Thus, while LNG appears to show a decrease in observed pregnancies, the Yuzpe regimen showed an overall pregnancy rate within the range of pregnancies that would occur if the women had received no treatment at all.

Let us revisit some of the compounding error factors that arguably are overstating the effectiveness of EC. First, the pregnancy probability estimates are most likely too high. The baseline studies selected couples with a higher than average fertility rate and whose sperm exposure was unhindered or even clinically enhanced. Wilcox's 2001 model established probabilities that were as much as **50% lower** than the Dixon model right at the most critical days in the cycle. But even Wilcox's probabilities are biased toward too high a number.

Second, attempting to identify each subject's day of the cycle creates another error. There are three elements that contribute to this second error. The first element is the assumption that women with "regular" cycles can be predicted to have a cycle of a given length. This simply is not the case. This 'guesstimated' cycle length date is used as the basis to subtract an assumed 13

or 14-day luteal phase, which creates another error factor. Finally, there is some evidence to suggest that only half of the women seeking EC are certain of the day their cycle began, a third error element.

Thus, it is not surprising that the Espinos study found the identification of the fertile window off by a factor of 2. Severi found a 50% error rate. If these error rates hold across the numerous studies on EC efficacy, the presumed effectiveness of EC would have to be cut by one-quarter to one-half. Compounded with the overstated pregnancy probabilities, researchers were concluding that many pregnancies were prevented by EC when, in actuality, those pregnancies never would have occurred even in the absence of treatment.

Addressing only one of the noted error factors - lowering the pregnancy probabilities - Trussell in 2003, lowered estimates of effectiveness for two studies from a range of 59.3% to 66.9%, to a range of 48.8% to 66.0% (Table 1). This is a significant drop from the early effectiveness ratings among the studies in the 70th and 80th percentiles. If Espinos' findings are reasonably accurate, Trussell's 2003 effectiveness rates might actually be only in the 25% to 33% range. In a 2004 article co-written by Trussell, the authors again acknowledge the potential for error in the formula for projecting pregnancies by stating, "The magnitude of this potential error is unknowable but could be very large." [35]

The critical point about EC effectiveness with regard to the abortifacient effect is that the presumption of the effect comes mainly by a logical extension of these very high (and now suspect) effectiveness rates. If EC are 60% to 74% to even 85% effective, undoubtedly a substantial number of the women taking the EC would have done so after ovulation, and the high effectiveness rate could only be attributed to post-conception effects. Prolife physicians (Kahlenborn, Stanford, Larimore) writing on the EC-abortifacient effect conclude, "The reduced rates of observable pregnancy compared with the expected rates in women who use hormonal EC in the preovulatory, ovulatory, or postovulatory phase are consistent with a postfertilzation effect, which may occur when hormonal EC is used in any of these menstrual phases."[36] Other researchers who found limited evidence of an abortifacient effect opined:

> "Our results leave a puzzling gap in our understanding of the mechanism of action in this therapy. Considering that the maximum fertility occurs on the days in the cycle when women were treated in our study, in order for the Yuzpe regimen to be able to prevent 75% of expected pregnancies, it must have some contraceptive effect [sic] when taken on or after those days."[27]

This study also referred to this as an "endometrial contraceptive effect," which of course, is not contraceptive at all, but abortifacient if it exists.

If the true effectiveness, however, is dramatically lower, then the possibility of a very limited, or even no abortifacient effect has to be examined. Both the original high effectiveness rates and the presumed abortifacient effects are all conclusions based on ***statistical projections***. The discussion to follow focuses on the available ***empirical evidence*** as to whether a "hostile endometrium" results from EC use and contributes to the "effectiveness" rate via early abortion.

PART II: Physiological Effects of EC - Are they abortifacient?

Ethical Breeches in Research

The development and use of EC, and the research into how they work, have followed an unethical and scientifically illegitimate path since the early 1970's. The sense one gets from reviewing the literature is that women have been used as guinea pigs with a recurring pattern of trial and error and that researchers did not express, in advance, a firm hypothesis as to what the newest test medication would do or why it produced the results it did. In essence, "Let's try this and see what happens" was the mode of operation. Much of the "research" literature is little more than a report and assessment of "what happened," with some speculation as to why. It is more akin to "experimentation" than research.

For example, one would expect that at least certain aspects of this research would have gone through significant laboratory and animal model testing before being applied to human subjects. But the literature reviewed here makes little reference to such research. This is highlighted by the fact that after four decades of research in this area, the first studies on how EC affects typical animal subjects (rats and monkeys) has only been done in the past few years (since 2003). As discussed later, these studies have proven to be very informative and beg the question: "Why wasn't this research done ***first***, before women became test subjects?"

The trial-and-error research approach has created a body of research literature that is strewn with poor design models and faulty assumptions, which have resulted in misguided and overstated conclusions. Had researchers followed the ethical and scientifically legitimate process of animal model testing first, they would have far more quickly found the limited effectiveness of EC. In fact, some of these drugs may have never been tested in women if these limited effects had been properly identified first in animal studies. As it is now, there is more public misinformation than accurate information.

A significant deficiency in the literature on EC is that the various studies independently examine only one or two aspects of the impact of EC, without thoroughly analyzing the entire physiological process and impact of EC. For example, one study reviewed below shows the impact of Yuzpe regimen on ovulation when administered across the follicular stage. However, the study does not measure the effects on the endometrium. Likewise, another study focused on endometrial effects, but it did not administer the treatment in the early follicular stage. Of course, hindsight is 20/20, and some research lacks solid design due to funding limitations. Yet, the presence of much more systematic and thorough research beginning in the mid-1990's demonstrates the weakness of the first few decades of EC research compared to the way research is done to cure diseases, for example.

Physiological Model for Effective Postcoital Treatment

As noted, the major foci of post-coital pregnancy disruption is to prevent either ovulation,

fertilization, or implantation. It is important to keep in mind the three essential hormones that govern the fertility cycle, and nature of the different drug regimens that are used as EC to disrupt that cycle. LH (leutinizing hormone) is key to stimulating ovulation. Estrogen triggers LH while prompting development of the endometrium (proliferative stage) and cervical mucus, and progesterone transitions the endometrium for implantation (moving it to the secretory stage). There is a myriad of other hormones and compounds that play critical roles in the fertility cycle. As couples who have experienced infertility come to learn, the interworking of these biochemical agents is complex and their balance can be delicate.

The Yuzpe regimen uses both estrogen and progesterone based compounds. While its estrogen side would do little to disrupt LH surge or endometrial proliferative development, its progesterone component seems a likely source for LH disruption. This is confirmed by the fact that LNG (Plan B) is a progesterone-only compound that has been found effective in disrupting ovulation, but appears not to affect the endometrium if ovulation does occur. Intuitively this makes sense, as progesterone is the key hormone for sustaining the endometrium after ovulation. Hence, giving progesterone-based Plan B after ovulation could actually serve as a supplement to endometrial development.

In a study on the effects of estrodiol and levonorgestrel, Nilson et. al, (1980) found that menopausal women exposed to estrogen went from having slight proliferative endometrial features (few ciliated cells and few and short microvilli) to more proliferative features. While fertile women exposed to progesterone had a decrease in proliferative features (more ciliated cells to fewer, and shorter, less-developed microvilli).[37]

Finally, RU-486 is an 'anti-progesterone,' meaning it blocks the progesterone receptors that are essential to endometrial receptivity. It is not surprising that this compound, which is antithetical to these natural hormones, has the ability to disrupt both ovulation and endometrial development.

It is crucial to remember that the fertile cycle is a very sequential process. A disruption, or lack of a disruption, at one stage of the process will have predictable effects later in the process. Thus, if estrogen expression is inhibited, normal endometrial development would not be expected. But neither would the LH surge be expected, nor ovulation. Likewise, if estrogen expression and LH surge lead to ovulation, endometrial development would be expected to occur as well. Similarly, progesterone exposure before ovulation could readily be expected to disrupt LH surge, ovulation, and endometrial development. But progesterone would not be expected to degrade or inhibit endometrial quality if given after the proliferative stage (post-estrogen exposure). At present, there is no physiological model offered that would contradict this sequential pattern.

Thus, there is no logical or theoretical model to substantiate the "hostile endometrium" proposition that every aspect of the fertility system works properly (FSH, estrogen, cervical mucus, LH surge, ovulation, conception) ***except*** the endometrial development and implantation after EC treatment.

EC Disruption of Ovulation

The degree to which EC disrupts ovulation (in a truly contraceptive manner) is crucial to the question of EC effectiveness and the abortifacient effect. The growing body of data regarding ovulation disruption shows the following pattern:

> If EC is taken the day before or the day of ovulation (late follicular stage), they have no impact on preventing ovulation. If EC are taken earlier in "follicular phase" - approximately 2 days to a week before ovulation - the normal ovulation pattern is interrupted. Frequently, however, it is only delayed, with ovulation and menstruation happening later than expected. If this interruption delays ovulation for the presumed 5-day sperm life, thereby eliminating possible fertilization from the unprotected intercourse, EC would serve effectively as a contraceptive.

One of the earliest studies on LNG by Landgren, et. al. (1989), had subjects taking one dose of LNG (0.75 mg) on each of 4 days at various times in the pre and periovulatory phases (double the total Plan B dose, but spread over 6 to 7 days rather 12 hours). Treatment very close to or after ovulation had no effect on preventing ovulation, but treatment in the early follicular phase did consistently delay ovulation.[25]

One of the earliest well-designed and thorough EC studies (though small in number) was conducted by Swahn, et. al., in Sweden (1996).The Yuzpe regimen was administered both before and after the LH surge. In the control cycles, all the subjects experienced their ovulations around day 15 (mean 15.6 +/- 2.1 s.d.). In the pre-ovulation treatment, all the subjects were given the treatment on cycle day 12, which hormone analysis later confirmed was prior to the LH surge. The LH surge was delayed 10 days to a mean of cycle day 25, with 3 of 8 subjects showing no LH surge (ovulatory dysfunction). Also, the mean cycle length was extended from 27 days (control) to 32 days (treatment). When treated 2 days after the LH surge, there was no measurable impact on ovulation or cycle length.[22]

Durand, et. al. (2001), published similar findings with four groups of women taking LNG at four different stages prior to and following ovulation. Disruption of ovulation only occurred among women taking the EC earlier in the follicular stage. Ovulation was not inhibited in those women taking it too close to ovulation.[28]

Hapangama, et. al. (2001), also found that taking Plan B very near ovulation did little to prevent ovulation. Despite some acknowledged shortcomings in pinpointing the time of ovulation, this study found that 5 of 12 (42%) women did not ovulate; the other 7 did. This led the researchers to speculate that if the true effectiveness rate of EC is in the 40% range, the entire effect of EC could be contraceptive. They then proceed to list many of the problems about actual EC effectiveness identified in Part I above and state that "it is possible that the genuine effectiveness of LNG as emergency contraceptive is less than **42%**."[29]

In an extremely well-designed, carefully conducted study, Croxatto, et. al. (2002), established the

cycle stage of each woman relative to ovulation by using transvaginal ultrasonography (TVU) to measure the size of the dominant follicle. Test treatments and placebos were administered to different cohorts at three pre-ovulatory stages, when the dominant follicle measured at 12-14 mm, 15-17 mm, and 18-20 mm, respectively. Once a follicle reaches the >12 mm stage, ovulation is generally anticipated within 5 days. If EC is found to disrupt ovulation for at least 5 days, then sperm exposure from intercourse would no longer be capable of causing fertilization.

The results showed that the Yuzpe regimen given at the latest follicular stage (within 2 days of ovulation), 18-20 mm, had virtually no impact on preventing ovulation. During the next 5-day period, all the women ovulated. By contrast, 50% of the women did not ovulate over the next 5 days when treated at the 15-17 mm stage, and 80% did not ovulate within 5 days when treated at the 12-14 mm stage. In the placebo cycles, 90% of the women ovulated during the 5-day period beginning at the 15 mm stage, and 77% given a placebo at the 12-14 mm stage ovulated during the 5-day period. Thus, if the EC was given too close the time of ovulation, it was "too late" to inhibit ovulation.[26]

Croxatto published a similar study in 2004, this time testing the standard two-dose LNG (Plan B) regimen and a single-dose treatment The study measured both follicle rupture and ovulatory dysfunction (where the follicle ruptures, but there is either a blunted LH surge and some type of dysfunction in luteal hormonal activity). The results were even more consistent than the Yuzpe regimen produced. For those treated earliest (12-14 mm follicle), 97% had either no follicle rupture or had ovulatory dysfunction in the 5 days after treatment. For those treated later (18-20 mm), 57% had no rupture or had ovulatory dysfunction during the 5-day period. The team of researchers concluded,

> "When LNG is administered after onset of the LH surge, it appears to have no effect on the ovulatory process, and this may explain the reported failure rate of this method....Conversely, when LNG was given before the LH surge, the surge was completely suppressed or blunted or its temporal relationship with follicular rupture was abnormal."[38]

Croxatto was also part of two teams of researchers who published the first significant animal model studies (rat and Cebus apella monkey) looking at the effects of LNG. While the studies were focused primarily on endometrial effects (to be discussed later), both found that treatment with LNG prior to LH surge prevented all or nearly all ovulations. But treatment after the LH surge had virtually no effect on ovulation.[39, 40]

In a study designed to essentially replicate the 2002 Croxatto work using TVU, Marions, et. al. (2004), administered the Plan B regimen at 2 days prior to the LH surge. Though it was a small study of only 7 women, none of the 7 ovulated subsequent to treatment. The same women were given RU-486 at LH-2 in another cycle and, again, none ovulated. In the control cycles, all the women were ovulatory.[41]

Gemzell and Marions then published a comprehensive review of these and other studies on LNG, summarizing what is now "conventional knowledge" on Plan B's ability to suppress ovulation:

> "The 'window of effect' for levonorgestrel seems to be rather narrow. It begins after selection of the dominant follicle [post-FSH], but before LH begins to rise. Levonorgestrel does not affect endometrial development or steroid receptor expression in the Fallopian tube. Animal studies confirm that levonorgestrel acts to block or delay ovulation, but does not affect fertilization or implantation."[42]

A critical implication for this conclusion, if it is true, is that hundreds of thousands of women are taking EC when it will have little or no effect. **This is unethical medical practice on a massive scale that borders on fraud. Indiscriminately giving EC to women without reasonably determining what phase of their cycle they are in seems to be little more than profit-motivated exploitation of women feeling desperate from fear of pregnancy.**

It is also important to indicate that studies have shown RU-486, in low doses (10 mg), given prior to LH surge, has the same effect on suppressing ovulation without affecting the endometrium. However, another RU-486 regimen of 200 mg given at or after ovulation shows a substantial effect on the endometrium and points strongly to an abortifacient effect.[3, 4, 42] Even though RU-486 may work in a contraceptive manner in this narrow window, it is clear that it remains an abortifacient if utilized when ovulation has occurred and conception is possible. **The prolife movement must remain insistent that use of RU-486 as EC is an abortifacient assault on nascent human life.**

Potential Postfertilization-Abortifacient Effects of EC

To presume or conclude that EC has an abortifacient effect, there has to be evidence showing that EC alters the endometrium so as to make it less receptive ("hostile") to the implantation of a conceived child, assuming the EC has failed to suppress ovulation or is given after ovulation. **The conclusions of researchers to date, and presented below, indicate that neither the Yuzpe regimen nor LNG (Plan B) necessarily render the endometrium hostile when ovulation has occurred. It is important to note that there have been effects on the endometrium identified, and that even among the authors who conclude that these effects were not significant enough to block implantation, they all leave open the possibility that an abortifacient effect <u>could</u> still come into play.**

Pro-EC researchers have done nearly all of the research on EC, and have become very sensitive to the political and religious implications of the abortifacient effect. This concern has been openly introduced into their research. Thus, studies published beginning in 2003 unabashedly admit that proving that EC are not abortifacient is an important goal of their research. This admission should raise the level of scrutiny the prolife movement applies to reviewing and critiquing these studies. The Croxatto-Muller team from Chile are affiliated with a Catholic university there, and clearly reflect a religious, even prolife, sensitivity. Here is a rather stunning admission in the introduction of one of their published studies.

> "The main question is centered on whether or not EC prevents pregnancy by interfering with postfertilization events. This issue is of importance for many people, considering that a new human life begins at the time fertilization is completed. Accordingly, interference with postfertilization events would lead to loss of human life."[39]

Meanwhile, the Marions-Gemzell team from the Karolinska Institute in Sweden express an even more blatant, agenda-driven motive:

> "However, neither of these EC methods [Plan B, RU-486] is available for a large portion of women because they are sometimes regarded as abortifacients, and, therefore, due to religious and political reasons, considered unacceptable in some countries. It is of great importance, for that reason, to further contribute to the clarification of the mechanism of action of LNG or MIF for EC, and eventually show that they do not act as abortifacients."[41]

Again, a healthy level of skepticism should be applied to the data and conclusions of researchers who blatantly direct their research toward a specific outcome.

The earliest research on the effects of EC on the endometrium certainly pointed to the potential for an abortifacient effect. Several of these studies, however, had significant design flaws. One study did endometrial biopsies only 3 days after ovulation, when it would not be expected to show entirely fertile qualities.[21] Thus, it was measuring the condition of the endometrium 3 to 6 days prior to implantation. Another study measured effects on women who self-administered 4 to 6 times the normal EC dose with no scientific controls over the treatment.[24] These results would not be applicable to the current research. In yet another study, the results for two different test groups were merged, thus making varying results indistinguishable between the groups.[19] In still another study, the EC dosage was given very late in the cycle, far past the fertile window, and even beyond the implantation window.[30]

The prolife movement ought not cite nor rely on these older, flawed studies as proof of the abortifacient effect. [See endnotes Ling, Kubba, Ugucsi, Taskin] Likewise, reliance on studies of birth control pills that show effects upon the endometrium is also untenable for two reasons:
1) EC dosages, and in particular the progesterone-only Plan B, are not directly comparable to the steady dose exposure of regular birth control use (particularly given the predominance of the estrogen-progesterone combined hormonal formula used today).

2) Studies that examine the endometrial response to a breakthrough ovulation in "on-Pill" cycles are either nonexistent or have escaped detection by this author.

The above proviso is **NOT** meant to conclude that the abortifacient effect does not occur in regular hormonal birth control use (including Norplant and Depo-provera injections). On the contrary, it highlights the fact that claims about hormonal birth control lack the most critical scientific information for making claims in either direction.

Looking at the physiological model, if "the Pill" prevents ovulation, we would expect impaired endometrial development. This author has yet to identify any study that has taken endometrial biopsies of women experiencing breakthrough ovulations while on the Pill. This is particularly relevant given the following body of research that ***has*** studied endometrial biopsies for the effects of EC in cases where treatment was given before and after ovulation, as well as in cases where ovulation was suppressed or failed to be suppressed.

The remainder of Part II will review the studies that have looked at the effect of both the Yuzpe and Plan B regimens on the endometrium, as well as other potential postfertilization effects that would threaten conceived children's natural development. Part III will retrace only the Plan B studies and identify in detail the specific parameters, criteria, measurements, and conclusions for each study. ***The information in Part III requires analysis and critique from those in the medical and scientific communities with the expertise to evaluate the integrity of the research and the stated conclusions.***

One of the earliest meaningful studies to look at endometrial biopsies after Yuzpe treatment was conducted by Ling, et. al. (1983).[20] Ling had published an earlier study in 1979,[19] but as noted above, its design structure was flawed, mixing the results of separate test groups, thereby rendering the study's results questionable. The 1983 study corrected many of those flaws but, without explanation, biopsies were conducted on only 6 of 12 subjects. Biopsy results showed detectable effects on the endometrium at the epithelial and stromal level. Namely, researchers found "slight" to "marked" lags in epithelial development and asynchronous development compared to the stromal components in 4 of 6 subjects, with 2 subjects showing no significant alterations.

The analysis of the biopsies was a microscopic visual observation level. The published results did not distinguish or correlate the results of hormone level analysis for all 12 subjects to the 6 subjects who were biopsied, nor in contrast to the 6 who were not biopsied. Despite these design shortcomings, this study provides evidence that the endometrium is negatively affected in some women. The researchers conclude, "This temporary disturbance of early events in endometrial development is probably sufficient to prevent the derivation of subsequent conditions required for successful implantation."[20] In essence, the slight endometrial disruptions identified here would lead to a disruption of later endometrial development, which could in turn be abortifacient.

In the Landgren study (1989), doses of LNG failed to prevent ovulation when given too close to ovulation. Endometrial biopsies were taken from 24 subjects, with numeric evaluation criteria established (number of glands per observation field, diameter of glandular lumen, and height of glandular epithelium). Though variations were found at this glandular level compared to the control biopsies, the study concluded, "[o]nly minor effects in the endometrium were observed during treatment."[25] The researchers did not find sufficient evidence to presume an abortifacient effect occurs.

Like the Ling study, Swahn (1996)[22] took biopsies only for the Yuzpe regimen given after ovulation so as to accurately estimate the implantation window and measure the endometrium at

that point. No biopsies were taken with the pre-ovulatory treatments because predicting ovulation and the implantation window would require more monitoring than the study (resources) allowed. Similar to the study by Ling, Swahn found "morphometric dating did not differ considerably from the chronological dating, but a significantly increased number of vacuolated cells and a wider diameter of glandular lumen than in the control cycle was seen." These later two parameters may actually describe an endometrial promotion effect, as they are the exact opposite finding of the negative effects on the endometrium caused by RU-486 given in the post-ovulation period.

The normal changes and developments expected to occur in the endometrium did so on schedule, with some changes in the structures of the endometrium. But these changes were "not significant enough to characterize the endometrium as out of phase." Swahn concluded, "[t]he relatively minor changes in endometrial development does not seem sufficiently effective to prevent pregnancy."[22]

Raymond, et. al. (2000)[27] studied endometrial effects of the Yuzpe regimen on women taking the medications on the day of, or the day after ovulation, as measured by LH surge. Endometrial biopsies were taken 8-10 days after LH surge and examined for expression of $\beta 3$ integrin, leukaemia inhibitory factor, glycodelin and progesterone receptors. Again, the "late" administration of the treatment resulted in no ovulations being delayed. The key factors of endometrial receptivity listed above did not show significant alterations that would prevent implantation. There were, however, statistically significant changes were found in MUC-1 expression, endometrial oestrogen receptor, luteal phase serum oestrogen concentration, reduced endometrial thickness, and greater proportion of glandular supranuclear vacuoles. But researchers did not find these factors to be outside the parameters of a receptive endometrial condition. They concluded that taken within +/- 1 day of ovulation, "there is no substantial evidence" that Yuzpe regimen "prevents ovulation, alters endometrial structure, or consistently affects endometrial proteins thought to be associated with uterine receptivity."[27]

The Marions study (2002)[4], using the transvaginal ultrsound/follicle measurement techniques, took endometrial biopsies at the time corresponding to implantation. Several markers of endometrial receptivity were assessed, including the expression of cyclooxygenase-1 and 2 (COX-1, COX–2), expression of the integrins $\alpha 4$ and $\beta 3$, progesterone receptor concentration was measured, as were secretory components. For women given Plan B at LH-2 and LH+2, 4 of 5 subjects showed no signs of altered cycle length, with the one woman's cycle being shortened by 7 days. Among the 5 subjects, 3 showed ***no signs of any*** endometrial changes. The subject with the shortened cycle could not be biopsied because her menses had begun. The remaining subject had insufficient tissue for collecting a biopsy sample.

As a group, they did not display a consistent pattern of significant alterations to one or more receptivity markers which would suggest an abortifacient effect. Thus, for Plan B administered around the time of ovulation, Marions concluded that the mode of action "is primarily due to inhibition of ovulation rather than inhibition of implantation."[4]

The Durand study (2001)[28] administered Plan B in both pre- and post-ovulatory phases, with endometrial biopsies taken at day LH+9. Ovulation was confirmed by TVU/follicle rupture to insure the actual implantation window was properly established. Evaluation of the endometrial biopsies found no significant effects on receptivity. The authors noted that "the predecidual changes as evaluated by the presence of prominent spiral arteries, which are considered crucial for implantation, were not altered by LNG." The endometrial samples were found to be consistent with chronological dating within 2 days (non-significant differences).The researchers further determined,

> "In this study, the process of transformation of endometrium into decidua, as a consequence of endometrial cell differentiation independently of conception occurred normally in women receiving LNG at the time of or after the occurrence of LH surge. In this regard, the existence of edematous changes along with development of prominent spiral arteries in LNG-exposed tissues strongly suggest the apparent preservation of endometrial structures thought to be associated with implantation capabilities."[28]

This is the first study to mention and test the prominence of spiral arteries. There is no comparison offered of the spiral artery examination to other glandular/stromal/epithelial characteristics found in other studies. Without this comparison, it will require expert analysis per Part III, to determine if these results are conclusive in contrast to the older studies.

In 2003, the Croxatto team published a review of the research to date on postfertilization effects as a means of previewing two animal model studies they were completing and preparing for publication. Croxatto reviewed, as above, the early studies that showed some signs of endometrial effect, but noted the lack of conclusiveness. They then noted the later studies reviewed above found no or only negligible alterations to the endometrium. In regard to Plan B, they concluded, "Full publications in refereed journals do not support the hypothesis that it alters endometrial receptivity or impedes implantation."[43]

Also in 2003, this Chilean team published results from a comprehensive study on the effect of LNG on laboratory rats. The rats were given doses 4 times higher than given in the typical Plan B regimen. The treatments were given in every conceivable time frame and scenario in order to test the abortifacient effect (pre-and post-ovulation, pre- and post-mating, pre- and post-implantation). As with the human studies, if given early enough in the follicular stage, ovulation was successfully prevented or delayed. However, there was virtually no difference in fertilization rates and implantation rates between the control group and the treatment groups when ovulation did occur. Regardless of when the treatment was given, the number of eggs ovulated, the number of eggs fertilized, and the number of embryos implanted were nearly identical to the controls. While the researchers admit that there are limits to the transferability of these results to the abortifacient effects in women, they could say *conclusively that a quadruple dose of Plan B is not abortifacient in rats*.[39]

In 2004, the same team published results of studies using Cebus appella monkeys. As with previous studies, a quadruple dose of Plan B limited ovulation if given early enough in the cycle.

But once again, the number of pregnancies was identical for those treated after mating with a placebo and those treated with a quadruple dose of Plan B. *The researchers could say conclusively that no abortifacient effect can be found with a quadruple dose of Plan B administered in Cebus apella.*[40]

Durand, et. al. published another study in 2005,[44] again looking to explain postfertilization effects because of the *presumed* high rate of effectiveness, including treating in the post-ovulation phase. This study measured the expression of glycodelin in the blood and endometrial tissue after Plan B. Glycodelin-A is a progesterone-regulated glycoprotein that has two known effects in the fertile cycle. Glycodelin-A has been found to be a potent inhibitor of the binding of sperm to the zona pellucida (outer membrane of the egg). It also affects the immuno-supporessant factors of the endometrium needed to prevent immuno-rejection of the embryo.

Glycodelin-A is absent from the endometrium during the first week of the luteal phase (through the implantation window), but is highly expressed in the second (last) week of the luteal phase. The authors speculate that early expression of glycodelin in cycles shortened by Plan B treatment could interrupt the immuno-suppressant factors during the implantation window. This suggestion is speculative given that glydcodelin expression is present and increasing at the end of the implantation window of a normal cycle.

Almost in passing, the authors note that biopsies taken at LH+9 showed ***no developmental asynchronization in the glandular-stromal components.*** The authors found virtually no effect on glycodelin expression when treatment was at LH surge or LH+2. For treatment at LH-3 or -4, the luteal phase was shortened and glycodelin expression started at approximately LH+2 (4 to 5 days early) and reached the highest expression an average of 4 days earlier than the controls. Progesterone concentrations in the blood were also markedly reduced in this group. The authors do not conclude that either the sperm-binding effect or immuno-suppressant effect can be verified by this study.[44]

A key element absent from the discussion of glycodelin expression, however, is the issue of timing with regard to its potential effects. A woman taking Plan B just 1 day after intercourse, and 3 to 4 days prior to LH surge, would have very few, if any, viable sperm present for fertilization by the time ovulation even occurs (12 to 48 hours after LH surge). A woman taking Plan B two or three days after intercourse, and 3 to 4 days before LH surge, would arguably have no chance of conception anyway. Even if there were ovulation and conception for Plan B administration less than 1 day after intercourse, and only 3 days before LH surge, the glycodelin expression does not increase significantly until after fertilization would have occurred, and it would not be at usually high levels by the time implantation would occur. Thus, the prospect of early glycodelin expression preventing conception seems numerically untenable. In essence, the researchers were hoping to find something, but the effects on glycodelin did not occur when they could have had any impact.

Other EC Effects

Some other noted or speculated effects of EC include shortened luteal phase in some women, spotting or bleeding episodes after treatment but before full menstruation, and potential decreased sperm motility if ovulation occurs one or more days after intercourse. If this third effect does occur, it would be entirely contraceptive in nature. But this is merely a speculative effect with no empirical evidence to support or disprove it.

A small number of the women in various studies did experience shortened luteal phases after ovulation. This suggests that the corpus luteum, (the follicle that released the egg) may not be functioning properly or its hormonal signal is being disrupted by the EC. Without the proper progesterone influences from the corpus luteum, the endometrium will not sustain itself and that would likely lead to the early menstruation. Most subjects displayed no hormone changes that would indicate decreased or stunted luteal function. Decreased luteal function seems neither to trigger concern among researchers nor prompt them to identify it as a potential abortifacient effect. This may be because shortened luteal phases appear to be a randomly occurring normal phenomena. Recall Wilson found that in studying untreated cycles, lutea phases for women with regular cycles could be as short as 7 days.[10] There is ***no evidence or theoretical explanation*** for or against this phenomenon being abortifacient. ***However, at present, it cannot be ruled out as a possible abortifacient situation for some women.***

Another consistent effect that is noted across many of the studies is that women whose ovulations are delayed experience spotting or bleeding episodes beginning 2 to 7 days after treatment, lasting 1 to 5 days. All the bleeding episodes are later followed by menstruation. None of the studies attempt to explain this phenomenon. Neither do the studies specifically correlate the findings of the endometrial biopsies with the women who experienced these bleeding episodes. Since all the biopsies tend to show minimal effects on key receptivity factors, the additional correlations are not discussed. Researchers seem to dismiss the bleeding since the endometrial biopsies later show fairly normal development.

In addition, some of the bleeding episodes occur even before ovulation (LH surge) occurs. This would be consistent with a phenomenon known as “breakthrough bleeding,” which can occur naturally in women who have an unexplained delay in ovulatory function. This type of episode does not reflect a hostile endometrium. In the natural setting, breakthrough bleeding might even reflect a heightened endometrial development. There is ***no empirical evidence*** to indicate exactly why these bleeding incidents occur in women taking EC and whether they contribute to an abortifacient effect.
Several studies have shown actually a few enhanced endometrial features after EC treatment. Swahn noted increased vacuolated cells and increased glandular diameter in certain subjects.[22] Landgren found increased number of glands or increased epithelial height.[25] Durand found an increased presence of stromal edema.[28] If the progesterone of Plan B influenced these enhanced endometrial qualities, it would be at least a theoretical basis for the “breakthrough bleeding” incidents. This condition, however, would not be something that contributes to an abortifacient effect.

Logical & Statistical Evidence Against Abortifacient Effect

One inescapable fact arguing against the abortifacient effect is the known failure rate of EC. As previously noted in Part I, women taking Plan B do get pregnant at a predictable rate. One is forced to conclude that whether administered before or after ovulation, EC fails either to prevent ovulation or prevent implantation. EC is clearly ***not*** abortifacient in some women. Many questions spring from this conclusion: Are only certain women vulnerable to the abortifacient effect due to their specific physiology while others are never vulnerable? Or are all women vulnerable, but only at given some other unknown factors that affect women in one cycle, but may not in others? Since EC does have a failure rate, and allows for successful implantation, what is the physiological model that makes this possible if the drug is presumed to have an abortifacient effect.

Also in conjunction the with the Part I conclusion that EC is not nearly as effective as is portrayed, is another point of logic regarding the abortifacient effect, namely - unintended pregnancies and abortions do not go down when EC is readily accessible ("over the counter"). Evidence to this effect is emerging in European countries and some select U.S. studies. Admittedly, if more women are engaging in unprotected sex and relying on EC as a back up, the built-in failure rate of EC could insure stable or increased numbers of abortions. more pregnancies and abortions. But that is the logical point, increased pregnancies or abortions equals the failure of a presumed abortifacient effect.

There is yet another statistical basis for arguing that EC is not effective as an abortifacient. If EC had a meaningful abortifacient effect, the effectiveness rate would remain the same through the 72 hours after intercourse that EC is recommended for use. One statistically significant study on the time gap between intercourse and EC treatment, and subsequent effectiveness, found an inverse correlation with nearly all of the pregnancies resulting when EC use is delayed by more than 1 day after intercourse (Piaggio, et. al, 1999).[31] This parallels the findings of von Hertzen and Van Look, where pregnancy rates for women using the Yuzpe regimen went from 2.0% for women taking the regimen within 24 hours of intercourse, to 4.7% for those taking it 49-72 hours after intercourse. For LNG use the pregnancy rate went from 0.4% (< 24 hrs) to 2.7% (49-72 hrs).[2]

To test this theory, Trussell, et. al. (2003) took their existing data bases from 8 previous studies and compared the presumed date of ovulation, the identified date of intercourse and treatment, and the number of pregnancies that resulted. The resulting statistical analysis provided the same general results as Piaggio and von Hertzen, that "failures" of EC happened more often when treatment was delayed.[32] These results were constantly touted in the now-successful drive to make EC available without a prescription, citing the need for women to have immediate access to EC to increase the effectiveness of the treatment.

It should be noted, that Trussell's statistical analysis can only be viewed as suggestive. First, it still has many of the built-in model flaws about effectiveness rates criticized in Part I. Thus, estimates of ovulation date, etc., make the numbers somewhat questionable. This is evidenced by

the fact that his model produces some estimated pregnancy rates that are lower than the actual rate of post-EC pregnancies. For these estimates to be true, it would suggest that EC actually increases the likelihood of conception for some women. This is, of course, an absurd result. Still, the degree to which the model points toward decreased effectiveness as EC use is delayed is substantial, would lead to the conclusion that EC is not effective as a post-conception abortifacient. If Trussell's analysis were applied to more accurate cycle-ovulation data, and this correlation were still found to be true, then the evidence would be much more instructive as to EC not being abortifacient.

Ectopic Pregnancy Risk

A final post-fertilization effect which is not abortifacient per se, but does pose a threat to the life of a conceived child, is the possibility that Plan B increases the risk of ectopic (tubal) pregnancy. Virtually none of the studies reviewed for this paper mentioned the incidence of ectopic pregnancy, while they do note the outcomes of any known pregnancies. There is every reason to assume that no ectopic pregnancies were found as pregnancies and all other adverse affects are part of the reports. Gemzell notes expression of steroid receptors in the Fallopian tube after LNG treatment.[42] However, a postmarketing surveillance of Levonelle (Plan B) use in England found an ectopic pregnancy rate of 6%, which is triple the normal 2% rate.[33]

In a strange, if not suspicious, set of circumstances, the review process by the FDA on whether to make Plan B available OTC apparently glossed over the potential increased risk of ectopic pregnancy. The FDA's Office of Drug Safety does a review of known risks and observed outcomes when approving any drug. When reviewing postmarketing outcomes of Plan B, the actual number of ectopic pregnancies observed is noted but never compared to the known number of total pregnancies observed after Plan B use. Thus, no ectopic to interuterine pregnancy rate has been offered.

The rationale/justification/excuse (this sequence is chosen purposely) for not calculating an ectopic rate is that it is difficult to discern the true number of pregnancies which occurred after EC use. Researchers/analysts state that ectopic pregnancies are more likely to be reported as an "adverse effect," whereas interuterine pregnancies might not be reported by women using EC because the pregnancy is viewed simply as a "method failure."One must assume the reported ectopic to interuterine pregnancy ratio is undoubtedly higher than the normal ectopic rate. And one certainly gets the impression that there is a reluctance to produce an ectopic rate compared with reported interuterine pregnancies as the news would not be favorable to EC promoters. If it were favorable, they would unhesitatingly offer that information.

Part III: Study Parameters, Criteria and Conclusions

Part II reviewed the relevant literature as to explicit endometrial effects of EC. Any analyst can review the literature, and can draw and summarize conclusions based on what is presented by the researchers. What is needed, however, is a critical review of study results themselves. Did the researchers choose the right parameters (or indicators) to observe? Are the measurement criteria

(statistical significance) meaningful and balanced? Are the conclusions consistent with the data and criteria selected? Prolife medical/scientific professionals with knowledge of physiology, cellular biology, etc., must step forward to provide this critical review. The following review of the relevant studies will be beyond meaning for the medical laity (this author included). Yet the critical review of these observation markers and criteria is the key to making objective conclusions about EC and the abortifacient effect.

Of the 7 studies reviewed in Part II that actually examined the condition of the endometrium after EC exposure (biopsies), only 3 involved Plan B (LNG).The other 4 studies involved either combined estrogen-progesterone pills, RU-486, or danazol. Given that Plan B has become the method of choice due to reduced side-effects, and is now to be available OTC, the primary focus of the EC-abortifacient debate will rest on the regimen for which there are only a scientifically sparse 3 endometrial human studies, plus 2 animal studies.

The 1989 Landgren study[25] of LNG involved an unconventional dosing of 0.75 mg on 4 predetermined days of the cycle, usually 2 days apart. No explanation is given for the varied dosing applied to treatment Group 3. The treatment was double the current Plan B dose, but spread out over 6 days, rather than 12 hours. The study sample involved 71 women in 3 countries, but endometrial biopsies were taken only from 22 subjects in one country (Sweden). The data are not presented in a way that separates out the Swedish women and then correlates their ovulatory and cycle effects with the specific results of their biopsies (though this information could probably be obtained from the researchers).

For the 22 Swedish subjects, 3 endometrial biopsies were taken somewhere in the window of cycle days 20-22 (pre-treatment control, treatment cycle, and post-treatment cycle). In the treatment cycles, however, two subjects did not have sufficient endometrial material to draw a biopsy sample, and one subject was menstruating (or possibly experiencing breakthrough bleeding). These three "missing" biopsies from the treatment cycles all came from groups 1 and 2. In essence, 30% of this small sample group were selected out of the treatment data. Thus, sample sizes within the 4 groups for the treatment cycle biopsies ranged from 3 to 6 (very small for statistical purposes).

Researchers measured 3 parameters over 10 random visual microscopic "fields" of each biopsy specimen, with a geometric mean established for each subject, and then geometric means for the 4 treatment groups. For each field, the number of glands were counted and the diameter of the glandular lumen was measured, as well as the height of the glandular epithelium. The results of these measurements are in Table 3, along with the data on the ovulatory/cycle effects for all 71 subjects. Again, because there is no correlation of the data between ovulation, or ovulatory dysfunction, and timing of the biopsy and condition of the endometrium, it is impossible to make causal inferences about the treatment's effect.

Table 3 - Landgren (1983) Plan B Data

Treatment Group	1	2	3	4
Cycle Days of Tmt	2,4,6,8	9,11,13,15	11,12,16,19	16,18,20,22
Group Size	N = 17	N = 17	N = 18	N = 19
Ave Cycle Length (Cntrl) 95% CI	27.9 26.3 - 29.7	27.7 26.4 - 29.1	27.6 26.2 - 29.1	27.0 25.9 - 28.1
Ave Cycle Length (Tmt) 95% CI	34.0 31.1 - 37.1	31.4 31.1 - 37.1	26.8 23.9 - 30.0	27.1 26.0 - 28.2
Ovulatory Function* Control/Treatment	17D/17D	17D/3B 7C 7D	18D/5B 6C 7D	19D/19D
Biopsy Group Size (Control/Treatment)	N = 5/N = 4	N = 5/N = 3	N = 6/N = 6	N 6/N = 6
# of Glands (Control) 95% CI	24.0 14.8 - 39.0	16.3 11.8 - 22.7	12.9 4.0 - 42.0	19.9 14.1 - 28.0
# of Glands (Treatment) 95% CI	9.5 2.8 - 31.9	22.3 10.0 - 49.8	19.0 11.9 - 30.4	15.4 9.2 - 26.0
Gland Diameter (Cntrl) 95% CI	46.0 28.8 - 73.5	62.1 44.3 - 87.2	52.1 45.1 - 60. 1	69.2 56.2 - 85.5
Gland Diameter (Tmt) 95% CI	25.0 22.0 - 28.3	33.6 19.9 - 56.8	46.3 31.8 - 67.6	52.1 32.3 - 84.19
Epithelial Height (Cntrl) 95% CI	19.1 16.5 - 22.1	18.3 13.7 - 24.5	19.1 15.6 - 23.4	19.4 16.1 - 23.4
Epithelial Height (Tmt) 95% CI	24.0 17.4 - 33.2	14.8 4.8 - 22.3	14.9 12.9 - 17.3	20.2 15.9 - 25.5

*The researchers coded ovarian function as follows:
A = Completely suppressed ovarian function
B = Follicular activity with complete lack of luteal function
C = Follicular activity followed by incomplete luteal function
D = Normal ovulatory function

The researchers' main conclusions on the endometrial effect are as follows:

"The main endometrial effects observed in this study, a decrease in number and diameter of glands when L-NOG was administered on cycle days 2, 4, 6 and 8 or 9, 11, 13 and 15, indicate that the proliferative activity of the endometrium is suppressed when L-NOG is administered during the follicular phase. When administered the secretory phase, L-NOG does not induce any significant endometrial changes."

Summarizing the key results: None of the women's ovulation was completely suppressed, though it was delayed in women receiving treatment early in the cycle (e.g. cycle lengths increased by

about 6 days in Groups 1 and 2). In fact, 50 of 71 (70.4%) women had normal ovulatory function in the treatment cycle regardless of treatment time, and only 8 of 71 women experienced complete luteal dysfunction. There was virtually no effect on cycle length for women receiving treatment in the late follicular or post-ovulatory stages, Groups 3 and 4.

As to the direct effects on the endometrium, in 2 groups the number of glands decreased and in 2 groups they increased. Likewise, epithelial height decreased in those 2 groups and increased in the other 2 groups. Glandular diameter decreased in all 4 groups.

Some critical considerations for this study include: the small sample size, the lack of correlation between ovulatory function and endometrial effects, and the endometrial biopsy timing. The researchers conclude that "proliferative activity of the endometrium is suppressed" when treatment is administered in the follicular phase (Groups 1 and 2). But this conclusion is based on biopsy taken during the treatment cycle at days 20-22, but cycle lengths were extended by 6 days in both of these groups. This is consistent with other studies that show that the proliferative-ovulatory axis can be delayed by EC treatment.

Thus, one would logically expect to find the endometrium to be less developed. Had biopsies been taken later in the treatment cycles, a more robust proliferative stage is at least theoretically possible. Again, directly correlating of the ovulatory and endometrial data for these two groups would be enlightening. This weakness in this study is accentuated by the attentive manner in which ovulatory function and endometrial evaluations were correlated in this next study.

Durand, et. al (2001)[28] tested the current Plan B regimen. There were 4 test groups receiving the doses at times related directly to hormonal-ovulatory events detected within the subjects. This research method of correlating treatment administration to identified fertility events within the subject greatly raises the quality of the study and substantially increases the ability to make causal inferences. As the researchers note:

> "This study was designed by taking into consideration the expected variability of the menstrual cycle among women and, therefore, the need to reassign the initially allocated participates into study groups by normalizing, within the cycle, the time of administration of LNG according to the onset of LH surge in serum. The rationale for the timed treatment schedule was also based on the probabilities of conception by cycle day as reported by Wilcox, et. al."

Initially the study was designed with 3 groups of 15 subjects to be given treatment at day 10 (Group A), at LH surge/peak (Group B) and LH surge + 48 hours (Group C), based on urinary LH levels. Blood samples were drawn, and transvaginal ultrasound was used to monitor the dominant follicle and observe for follicle rupture (ovulation). Later evaluation of the serum (blood) levels of LH found that 4 Group B subjects were 2 to 3 days short of LH peak, as were 4 subjects in Group C. These 8 subjects were put into a new Group D, classified as having treatment in the "late follicular phase." The researchers commented on the 13.3% "false positive" reading by urinary analysis as being a weakness in previous studies regarding timing for properly making endometrial observations within the implantation window.

Thus, biopses were taken at LH+9, and endometrial morphological dating was correlated to serum LH surge, estradiol, progesterone levels, and follicle rupture, but not to menstrual calendar dating. Microscopic visual evaluations were performed (the evaluator was blinded as to specimen and group identity). Histologic dating used the Noyes criteria, along with the Hendrickson & Kempson criteria. Glandular and stromal elements were dated using Lessey's criteria. A specimen in which glandular maturation delay was more than 2 days from LH surge date was considered "out of phase." Data are presented by the Mean +/- standard deviation, $p < 0.05$.

Because 12 of 15 subjects in Group A did not ovulate at all during the treatment cycle, they were eliminated from the endometrial analysis. The absence of ovulation significantly shortened the cycle length for these subjects (15 days +/- 2, compared to 26 days +/- 3 in the control cycle). For the remaining 3 subjects in Group A, ovulation did occur but was delayed by a mean of 3 days. The luteal phase was correspondingly shortened by a mean of 3 days. Thus, overall cycle length was unchanged in the three Group A subjects.

As with previous studies, administration of Plan B near or at ovulation did nothing to suppress ovulation in Groups B, C, and D. Follicular and cycle length were completely unaffected in Groups B and C. Follicular length was unaffected in Group D, but the luteal phase was shortened by a mean of 2 days (statistically significant $p < .05$). These data parallel the results of Group A, where treatment was earlier in the follicular stage as compared to Groups B and C.

Regarding the critical endometrial analysis, of the original 45 subjects, the 12 annovulatory Group A subjects were obviously excluded. Also excluded were the remaining 3 Group A subjects, and 4 Group D subjects because their biopsies were subsequently found to be taken on a day other than LH+9, based on later hormonal analysis. Two more subjects, one each in Group B and D, had insufficient tissue for biopsy sampling. Thus, 24 biopsy specimens from treated, ovulatory cycles were studied. None was found to be "out of phase" (more than 2 days chronological v. morphological). Of the measured parameters, the number of glands, presence of stromal edema, and presence of spiral arteries were not significantly changed (did not reach a statistically significant level). The researchers concluded:

> "These results also correlate with the presence of normal histopathological features in endometrial biopsies taken during the implantation window in women from Groups B, C, and D. Indeed, in this study, the process of transformation of endometrium into decidua, as a consequences of endometrial cell differentiation independently of conception occurred normally in women receiving LNG at the time of LH surge or after the occurrence of LH surge. ...These results suggest that postovulatory contraceptive efficacy of LNG may not involve alterations in the mechanisms associated with endometrial receptivity."

The one area of further research the authors suggested was in the mildly shortened luteal phase (2 days) of those receiving treatment in the follicular phase, with corresponding lower progesterone levels and possibly limited corpus luteum dysfunction.

Table 4 - Durand (2001) Plan B Data

Ovulatory function	Control	Group A	Group B	Group C	Group D
Treatment time	n/a	Day 10	LH surge	LH + 2	LH-2/3
Sample Size	N = 45	N = 3	N = 11	N = 11	N = 8
Cycle length (Cycle days)	26 +/- 3 (21- 34)	28 +/- 6 (21 - 32)	27 +/- 2 (22 - 29)	26 +/- 4 (23 - 28)	24 +/- 5 (17 - 32)
Follicular phase length (days)	15 +/- 3 (9 - 15)	19 +/- 2 (17 - 21)	15 +/- 2 (13 - 18)	15 +/- 1 (13 - 17)	14 +/- 3 (10 - 17)
Luteal Phase Length (days)	12 +/- 1 (9 - 15)	9 +/- 4 (4 - 12)	11 +/- 2 (9 - 14)	11 +/- 1 (10 - 13)	10 +/- 4 (5 - 16)
Follicle rupture (Cycle days)	15 +/- 2 (11 - 21)	18 +/- 4 (14 - 22)	16 +/- 2 (13 -18)	16 +/- 2 (13 - 19)	15 +/- 2 (11 - 18)
Endometrial Biopsy	N = 41	n/a	N = 10	N = 11	N = 3
# of glands/field	59 +/- 12	n/a	58 +/- 7	55 +/- 8	58 +/- 1
# of glands/mm^2	30 +/- 6	n/a	29 +/- 4	28 +/- 4	29 +/- 0.8
Stromal edema/mm^2	1049 +/- 308	n/a	1225 +/- 261	1,011 +/- 209	1,142 +/- 40
% tissue stromal edema	53 +/- 15	n/a	61 +/- 14	51 +/- 10	57 +/- 1.4
Spiral arteries/field	6 +/- 3	n/a	4 +/- 1	5 +/- 2	4 +/- 1.4

Compared to the Landgren study, this is a greatly improved study model. Still, some critical considerations for this study include: the meaning and interpretation regarding the 2 subjects who had insufficient tissue for a biopsy sample in the treatment cycle. There were 4 subjects who had insufficient tissue in the control cycle before treatment. If, as the researchers conclude, endometrial samples showed no significant signs of a 'hostile' environment, what is the cause of these 2 samples being insufficient in the treatment cycle? Are these 2 subjects among the 4 subjects who did not provide a sufficient biopsy sample within the control cycle? Also, why was the presence of spiral arteries chosen as a parameter? No previous or subsequent studies chose this marker.

Now to the third directly relevant study by Marions in 2002.[4] In this study, again the current Plan B regimen was tested along with a separate test of RU-486 (mifepristone) as EC. The sample groups were very small, only 6 subjects for each drug. The subjects were monitored first with a control cycle, followed by a treatment cycle give before ovulation, a resting cycle, then a second treatment cycle given after ovulation. Ovulation was detected using transvaginal ultrasound to monitor follicle development and rupture. Treatment before ovulation was given when the follicle matched the size of the follicle in the control cycle at LH - 2. Treatment after ovulation was based on a LH surge urine analysis (LH + 2). Endometrial biopsies were taken in the window of 6 to 8 days after LH surge. Morphometric data and immunochemistry staining of the

biospy samples were evaluated using the two-tailed Wilcoxon signed rank test, significance at $p < .05$.

The endometrial parameters measured included: number of glands, number of glandular and stromal mitosis per 1000 cells, glandular diameter, glandular epithelial height, basal vacuolized cells per 1000 glandular cells, number of pseudostratfied cells, and degree of stromal edema. These parameters were analyzed using an electron microscope. Immunostaining of the biopsies was done to measure expression of cyclooxygenase-1 and -2 (COX-1& 2); integrins $\alpha 4$ and $\beta 3$ were measured using polyclonal antiboides; progesterone receptor was measured using a monoclonal assay system. Scoring of the stained samples was done by two independent persons using a microscope.

Again, because treatment was administered at LH-2 or LH +2, all but one subject had normal ovulatory cycles. The nonovulating subject was excluded from the endometrial evaluation, so the sample size was reduced to 5 subjects. Cycle lengths were normal for 4 subjects, with 1 subject having a shortened luteal phase (7 days shorter). For both the pre- and post-ovulatory treatment groups, 3 of the 5 subjects had normal endometrial development. Among these, there were no significant differences in the parameters between the control and treatment cycles, with the exception of one subject having reduced COX-2 expression in the glandular cells. In the pre-ovulatory treatment, one subject had insufficient tissue for a biopsy sample. Further, the subject with the shortened luteal phase had already begun menstrual bleeding.

In the post-ovulatory treatment, 1 biopsy was found to be "out of phase" (more than 2 days). Again, reduced COX-2 expression in glandular cells was found in 1 subject (the same subject as above?), and reduced COX-2 expression in luminal cells in another subject. All other parameters for endometrial development in the post-ovulatory group were found to be similar to the control cycle. The researchers concluded that the mode of action for LNG (Plan B) is inhibition of ovulation rather than inhibition of implantation.

As with the previous study, what is the explanation for the insufficient biopsy sample, and what potential abortifacient effect is there for subjects with shortened luteal phases? For the one biopsy found to be "out of phase," was that possibly the result of a misdated "false positive" reading as discovered in the more accurate Durand study accounted for?

This study shows that normal cycle length and endometrial development are predominant after LNG administration, such that there would be no abortifacient effect for the majority of women. Research emphasis again must be placed on the question of subjects with insufficient tissue or shortened luteal phases. In the later case, implantation might even successfully occur, but be short lived as luteal dysfunction leads to an early menstruation - thereby a different variation on an abortifacient effect.

It is also important to reiterate that in the two animal studies, using dosages four times that of Plan B, there was virtually no abortifacient effect in either rats or monkeys. The number of eggs released and fertilized, as well as the number of embryos implanted, was nearly or virtually

identical between the untreated controls and the LNG-treated subjects under any timing of treatment where conception and an abortifacient effect would be possible. As simple statement of the research results, LNG had virtually no postfertilization effects in these two species.

A Final Consideration - Selective Vision

One of the apparent factors in the entire debate about the abortifacient effect of EC is the all-too-human factor of selective vision - we see what we want to see or what we are expecting to see. Or, as noted, with the erroneously presumed high effectiveness rate, there must be something to see. This writer is extremely sensitive to and, to a degree, worried about personal biases and selective vision as they may have affected the researching and writing of this paper. Many aspects of the research, and even the discussion language of the studies, hints at the biases and expectations that some of the researchers brought to their work or their conclusions. It is possible that some of the more recent research which dismisses the endometrial changes as "not significant" have been done with a goal in mind of making that conclusion. EC proponents are very sensitive to the abortifacient controversy, and they have strong political and financial motives for making that controversy go away. If the line of research finding various endometrial alterations, but concluding these alterations are not sufficient to render the endometrium hostile, was the hoped for result, then dismissing the alterations is a false representation. The endometrium may in fact be hostile.

As a policy analyst, I make no claim whatsoever to know anything about integrins, progesterone receptors, vacuolated cells, and all the other physiological and technical measurements of the endometrium that these studies discuss. Experts trained in this field must be consulted to determine if the tests, measures and findings were looking at the right factors, setting the proper criteria or thresholds, and making conclusions consistent with the data. Those are judgments for medical experts. We have such persons in the prolife movement, and they must be consulted.

What should be clear from the information presented here is that neither proponents nor opponents of the abortifacient effect can make a definitive, scientifically-backed conclusion in either direction. There are simply too many unanswered questions, too much uncertainty. For those who are morally opposed to abortion, they may legitimately continue to question the ***potential*** for an early abortion still exists. ***No one, however, should presume or claim that EC in fact, can cause early abortions***. With better information, and more detailed research, one day we will know the answer.

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