Research on New Methods of Emergency Contraception

By Helena von Hertzen and Paul F.A. Van Look

The term "emergency contraception" refers to specific contraceptive methods that can be used as emergency measures to prevent pregnancy after unprotected intercourse. Emergency contraception is used after coitus but before pregnancy has become established; as such, it is considered a back-up method for occasional rather than regular use.[1]

All methods currently available for emergency use have limitations. That they can only be administered within a few days after intercourse restricts their usefulness and disqualifies for treatment women who cannot meet this deadline. Moreover, the methods, and the hormonal regimens in particular—such as high-dose estrogen or combined oral contraceptive tablets (known as the "Yuzpe regimen")—may cause unpleasant side effects, including nausea, vomiting, headaches, dizziness and breast tenderness. These side effects can limit compliance and, in the case of vomiting, may affect the methods' efficacy.

Emergency methods are generally not as effective as other contraceptive methods. For example, even when the Yuzpe regimen is administered within the recommended 72 hours, it fails to prevent one-quarter of the pregnancies that would be expected without the therapy.[2] And although insertion of an IUD after unprotected intercourse is more effective and can be initiated later than the hormonal regimens (up until the expected start of implantation), its usefulness is limited because of the risk of infection, especially in victims of sexual assault or following intercourse with a new partner. IUD insertion is also not usually recommended for nulliparous women, and such women constitute a sizable proportion of those requesting emergency contraception.[3]

In addition to the drawbacks of these existing methods, their variety is very limited; a woman seeking emergency contraception has few choices at her disposal. Also, no currently available method is effective once implantation has commenced—unless endometrial aspiration is considered a method of emergency contraception.[4]

Emergency contraception could prevent many unwanted pregnancies. For example, a study carried out among 733 women requesting pregnancy termination in Oxford, United Kingdom, found that 410 women (56%) had had unprotected intercourse or experienced difficulty with the barrier method used.[5] Among these 410 women, 18 used emergency contraception without success; the remaining 392 did not use emergency contraception, mainly because they did not know it existed or where they could get it.

Had these 392 women used the Yuzpe regimen, about three-quarters of them would not have become pregnant.[6] Nevertheless, the fact that the Yuzpe regimen would not have prevented 25% of the conceptions among these women illustrates the very clear need for new and better methods of emergency contraception. In this article, we first explore what the ideal emergency contraception method would be. We then review those new methods that are now being tested and, finally, we conclude by outlining the prospects for improving emergency contraception in the future.

Ideal Emergency Contraception

Method Attributes

The most important requirement of the ideal emergency contraceptive is that it be highly effective. Women who seek emergency contraception definitely want to avoid pregnancy. If a method, such as the condom, has already failed, there is no place for another failure. Methods of emergency contraception also have to be as safe as other methods, even though they are used only occasionally. The ideal method should be free of side effects, although women may accept some side effects as the price to be paid for a high effectiveness. Furthermore, side effects caused by an emergency method may not carry the same weight as those caused by regular methods, since an emergency method may be needed only once in a lifetime.

The method would ideally not disturb the menstrual cycle, as a delay in menstruation would raise concerns that the method had failed and add to a woman's anxiety. Also, the longer the interval tolerated between unprotected intercourse and administration of the ideal method, the greater would be its practical value. An emergency contraceptive should provide full interceptive protection, preferably after a single administration. It should also be active in an easily administered form, such as an oral or vaginal tablet or a nasal spray. Finally, the method should be affordable: No matter how perfect emergency methods might be, they will not help people who cannot afford them.

A thorough knowledge of the physiological mechanisms that lead to pregnancy is indispensable for the development of new compounds or the identification of already existing ones that might be tested for their potential as emergency methods. To be effective, a method has to disrupt crucial events in the establishment of pregnancy. While unprotected intercourse may take place at any time during the menstrual cycle, pregnancy can only result from intercourse during the fertile phase—from about five days before until about 24 hours after ovulation, a period that corresponds to the life span of sperm in the female genital tract and the time during which the oocyte is fertilizable. The human blastocyst probably starts to penetrate the uterine mucosa by the fifth or sixth day after fertilization,[7] and implantation is completed—and pregnancy established—around the time of missed menses.[8]

While these facts are obviously relevant in considering emergency contraception, clinicians should always prescribe emergency contraception after unprotected intercourse, regardless of when it occurs in the menstrual cycle. Women's cycles vary, and even the most sophisticated laboratory techniques cannot determine retrospectively whether intercourse occurred in the fertile or infertile phase.

Mechanisms of Action

All emergency methods currently in use act before implantation. Theoretically, this could be achieved in several ways; in practice, however, the possible modes of action are more limited, because women re-

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quest emergency contraception at different times during their menstrual cycle. This variability in timing means that compounds that work only through disturbing ovulation or some event closely associated with it cannot be highly effective as emergency methods.

Figure 1 depicts how a drug's mode of action influences its potential value as an emergency contraceptive compound. A drug that acts during the follicular phase only—for example, by interfering with oocyte maturation or by blocking ovulation—would only be effective at preventing pregnancies that result from intercourse in the preovulatory phase, if the treatment is started soon enough before ovulation (see arrow A in figure).

Preventing fertilization rather than ovulation would be a potentially more useful approach, since the window of activity would be wider (see arrow B in figure). Such a compound's duration of action would need to be sufficiently long to remain capable of preventing fertilization, even if both unprotected intercourse and use of the drug take place early in the fertile period. However, if intercourse were to take place late in the fertile period, at about the same time as or shortly after ovulation, fertilization may not be successfully blocked. Spermatozoa reach the site of fertilization within a few minutes following intercourse,[9] and irrespective of whether these "early arrivals" comprise the spermatozoan most likely to result in fertilization, the likelihood of achieving an effective drug concentration in time at the fertilization site seems small, even if the woman were to start treatment shortly after coitus.

Thus, to achieve the highest possible efficacy, the ideal emergency contraceptive drug needs to act interceptively; that is, it should be capable of interfering with a physiological event that occurs after fertilization—during the period of early embryonic development prior to implantation (see arrow C in figure). Obviously, such interceptive protection must be achieved, even though drug exposure may be limited to a single occasion at the beginning of the fertile phase of the cycle.[10]

For the compound to target one particular postovulatory event, such as a critical moment in the endometrium's preparation for the implantation of the conceptus (known as nidation), it must exert its effect for the entire duration of the fertile phase, plus the time needed until the targeted event occurs. If it cannot achieve such a duration of action, the drug may need to combine preovulatory and postovulatory modes of action to be effective.

New Hormonal Approaches

Scientists have known about the importance of ovarian hormones in establishing pregnancy since the early 1930s, and most efforts to identify leads for emergency contraception have focused on these hormones. In the 1970s, the regular combined oral contraceptive was tested as an emergency method in what became known as the Yuzpe regimen. More recently, levonorgestrel alone was tested as an emergency method, and a number of studies have looked at the efficacy of danazol, a potent antigonadotropin and progestogen. Another approach has been to counteract those hormones presumed or known to be involved in the establishment of pregnancy—including estrogens, gonadotropin-releasing hormone (GnRH) and progesterone—through the administration of antihormones.

Levonorgestrel

Research undertaken mainly in the 1970s concluded that progestogens were unsuitable for regular postcoital use, primarily because they caused a high degree of cycle disturbance. However, some studies did indicate levonorgestrel's potential as an occasional method of postcoital contraception. One study, conducted among 50 fertile women in Hungary,[11] tested the efficacy of 0.75 mg of levonorgestrel administered immediately after intercourse that occurred around the time of ovulation.

There were no pregnancies in the 150 cycles studied (during which the women reported 163 acts of intercourse). Administering levonorgestrel during this phase of the menstrual cycle also did not seem to disturb the length of the cycle. Although the study did not reflect a real-life situation—the women's husbands were in the military and were allowed only limited visits with their wives, which corresponded to four days around the estimated time of ovulation only—it did give some indication of levonorgestrel's potential as an emergency contraceptive.

The first researcher to look at the efficacy of levonorgestrel as an emergency contraceptive gave 205 women a 0.6 mg dose within 12 hours after unprotected intercourse and compared the results with those in 525 women treated with the Yuzpe regimen.[12] About 3% of women in the levonorgestrel group became pregnant, compared with some 2% of the women treated with the Yuzpe method.

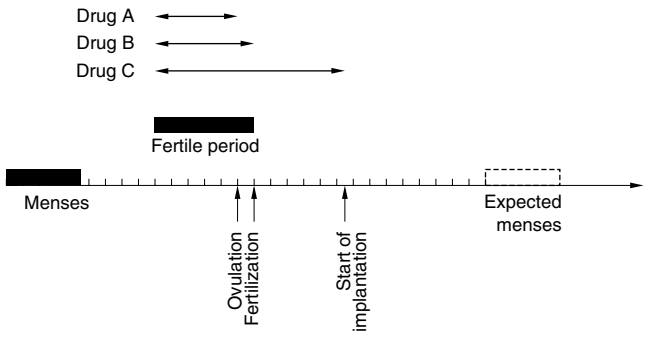
Because 0.75 mg levonorgestrel tablets are marketed in several countries for occasional contraceptive use, the World Health Organization (WHO) supported a prospective randomized trial conducted in 1991 that compared the effectiveness and side effects of two tablets, each taken 12 hours apart, with those of the Yuzpe regimen among women requesting emergency contraception within 48 hours of unprotected intercourse.[13] A total of 424 women were assigned the Yuzpe regimen and 410 women were given two 0.75 mg doses of levonorgestrel.

There were 15 pregnancies (3.5%) in the Yuzpe group and 12 pregnancies (2.9%) in the levonorgestrel group. After women who had had further acts of intercourse during the remainder of the treatment cycle were excluded (18% of the Yuzpe group and 19% of the levonorgestrel group), the failure rates were 2.6% and 2.4%, respectively. The incidence of nausea, vomiting and fatigue was significantly higher ($p<.001$) among women taking the Yuzpe regimen than among those given levonorgestrel.

These results suggested that levonorgestrel could be as effective as the Yuzpe regimen, but might cause fewer side effects. With both treatments, pregnancy rates tended to be slightly lower among women who initiated treatment within 24 hours after intercourse than among those who began after a longer interval.

If these findings are confirmed in a larger study, levonorgestrel could represent an improvement over currently available hormonal methods of emergency contra-

Figure 1. Timing in the menstrual cycle when emergency contraceptive compounds would be effective



Notes: Arrows indicate the period of compound's effectiveness. Drug A blocks oocyte maturation or ovulation. Drug B prevents fertilization. Drug C intercepts postfertilization events.

ception. WHO's Special Programme of Research, Development and Research Training in Human Reproduction is now conducting just such a study—a multicenter, randomized, double-blind trial that will compare the Yuzpe regimen and the levonorgestrel treatment when taken up to 72 hours after unprotected intercourse. The study is to include more than 2,000 women recruited by 22 centers in 15 countries, and the results are expected to be available in early 1997.

The few studies that have looked at levonorgestrel's mechanisms of action in postcoital contraception suggest that it may affect both follicle growth and development of the corpus luteum (the progesterone-secreting tissue that forms in the ovary immediately after ovulation). One study in which women received 1.6 mg of levonorgestrel on day 10 of their cycle showed that the treatment seemed to suppress the midcycle luteinizing hormone peak (which induces ovulation), but did not appear to influence the formation and function of the corpus luteum, since the urinary excretion of pregnanediol (the main metabolite of progesterone) was normal.[14]

"…any substance interfering with the synthesis, secretion or peripheral actions of progesterone has the potential for use in emergency contraception."

Another study, which examined the effects of a daily dose of 0.75 mg of levonorgestrel administered for four days either before ovulation, around the time of ovulation or after ovulation, indicated that the impact of levonorgestrel depends on the time of administration.[15] When levonorgestrel was given during the early follicular phase, the total cycle length was significantly prolonged due to the increased duration of the follicular phase. Post-treatment biopsies taken on cycle days 20–22 still showed proliferative endometrium in accordance with the delay in ovulation.

When levonorgestrel was administered around the time of ovulation, however, the effects were variable: Ovulation was blocked in some women, while in others follicular activity was followed by deficient luteal function, and still other women ovulated normally. On the other hand, administering levonorgestrel during the luteal phase did not affect cycle length or cause any significant endometrial changes. This last finding was somewhat unexpected in view of the proven effectiveness of levonorgestrel in emergency contraception. Clearly, additional research is needed to determine how levonorgestrel acts when it is administered after ovulation has already taken place.

Danazol

In the search for an effective emergency contraceptive that would cause fewer side effects than the Yuzpe regimen, danazol was tested in a study of 50 women who received two 400 mg doses 12 hours apart.[16] Three pregnancies occurred, yielding a failure rate of 6%.

The largest study to compare danazol with the Yuzpe regimen included 990 women assigned to an 800 mg dose, 730 women assigned to a 1,200 mg dose and 407 women who were given the Yuzpe regimen.[17] Women found danazol more acceptable than the Yuzpe method because it caused fewer, milder side effects of shorter duration. Moreover, both danazol groups had low failure rates (1.7% with 800 mg and 0.8% with 1,200 mg), although not significantly lower than that for the Yuzpe regimen (2.2%).

A more recent WHO-supported study failed to confirm these findings, however: Nine pregnancies occurred among 193 women treated with danazol (600 mg given twice, 12 hours apart), a failure rate of 4.7%.[18] The number of pregnancies observed in that study (nine) was nearly the same as the number that would have been expected with no treatment (12).

Further studies examining danazol's possible mechanisms of action suggest no clear effect on ovulation.[19] Data from an unpublished study revealed no midcycle peak in luteinizing hormone among four of eight women given 600 mg of danazol twice on day 12 of the menstrual cycle, while for the other four, the peak was delayed to a variable degree; ovarian steroid production was essentially unchanged, however.[20]

Furthermore, when women were given 600 mg of danazol twice, two days after the peak day of luteinizing hormone levels, biopsies showed no significant influence on endometrial structure 6–8 days after the peak. Other research also has been unable to demonstrate any significant effect of danazol on steroid receptor concentrations in the endometrium after two 400 mg doses of danazol at 48 and 60 hours after the luteinizing hormone surge.[21] Thus, questions about danazol's effectiveness and mechanism of action remain unresolved.

Antiestrogens

The potential value of antiestrogens in emergency contraception depends entirely on whether or not estrogen plays an essential role in implantation. In particular, until recently scientists did not know whether 17ß-estradiol, a steroid hormone secreted in large quantities by the corpus luteum, is essential for implantation in primates.

In an attempt to resolve this question, studies were carried out in rhesus monkeys involving the transfer of preimplantation embryos from donor mothers to monkeys from which the ovaries had been removed. (Some had their ovaries removed and were started on hormone replacement therapy on the day the embryo was transferred; others from which the ovaries had been removed earlier had hormonally induced artificial cycles.) The results suggest that, in the rhesus monkey, ovarian estrogen may not be necessary for successful implantation, since implantation took place and normal pregnancies ensued in some of the monkeys that were given progesterone alone and had undetectable estrogen levels around the time of implantation.[22] Recently, luteal estradiol was also shown to be unnecessary for the establishment of pregnancy in humans.[23] In view of these results, it seems unlikely that antiestrogens have a role in emergency contraception.

GnRH Antagonists

GnRH antagonists, which cause a profound drop in progesterone secretion because they suppress luteinizing hormone levels, have also been proposed for postcoital contraception. Recent research has shown, however, that low doses of human chorionic gonadotropin, which mimic early pregnancy, can prevent luteal regression induced by postovulatory administration of a potent GnRH antagonist.[24] The study also confirmed results from earlier research suggesting that in the absence of human chorionic gonadotropin, the action of the GnRH antagonist has to continue for at least 72 hours if the corpus luteum is to regress irreversibly; corpus luteum function will recover if the drug's action covers any shorter period.

These results suggest that to be effective as an emergency contraceptive, a GnRH antagonist would need not only to be

given soon after ovulation and before the blastocyst began to secrete human chorionic gonadotropin, but also to be continued for at least three days. If given too late (once implantation has started), the treatment would be ineffective; if given too early (prior to ovulation), the drug might not block ovulation and fertilization might occur (since shortly before ovulation, mature follicles are not very susceptible to acute gonadotropin withdrawal).[25] The window of efficacy, therefore, seems too narrow—and the mode of administration too complicated—for GnRH antagonists to be successful emergency contraceptives. Also, the cost of currently available antagonists would be prohibitive, and they have been associated on some occasions with allergic local reactions.[26]

Progesterone Inhibition

The common denominator in the chain of phenomena leading to pregnancy is the influence of progesterone. It is involved before ovulation, in follicular maturation and the process leading to ovulation;[27] it is a major constituent of follicular fluid and may be the component responsible for inducing the movement of spermatozoa to the ovum for fertilization;[28] it may also produce structural changes that facilitate the entry of spermatozoa into the ovum;[29] it influences the transport of the fertilized egg through the Fallopian tube and causes endometrial changes (known as decidualization) that are required for successful implantation and establishment of pregnancy; and it affects the function of the endometrial surface (the endometrial epithelium) and the interaction between that surface and its supporting structure (the endometrial stroma).

Thus, any substance interfering with the synthesis, secretion or peripheral actions of progesterone has the potential for use in emergency contraception. Compounds that fall into this category include substances that disrupt the corpus luteum (referred to as luteolytic agents), inhibitors of progesterone synthesis (such as epostane), and progesterone receptor blockers (such as antiprogestogens).

The maintenance of the corpus luteum is essential for establishing pregnancy; therefore, compounds with luteolytic action would be useful emergency contraceptives. However, research to discover such luteolytic agents has so far been unsuccessful.

Progesterone synthesis inhibitors such as epostane could be effective, as they interfere at several levels in the establishment of pregnancy. However, repeated doses for several days are likely to be needed to influence progesterone levels. In addition, because of potential controversy surrounding the use of these compounds in abortions, further research on the most advanced of these inhibitors has been discontinued by the company that owns the rights to them.[30]

Antiprogestogens act directly at the cellular level, by binding to the progesterone receptor and blocking the action of progesterone. Their influence is thus more immediate than that of progesterone synthesis inhibitors. While hundreds of compounds with antiprogestational activity have been identified, only a few have been sufficiently evaluated in biological screening models and only four—mifepristone, lilopristone, onapristone and CDB 2914 (also known as HRP 2000)—have been given to humans. Most antiprogestogen research to date has been on mifepristone (RU 486), but the results of this research should apply to most if not all antiprogestogens, with some minor modifications.

• *Mechanisms of action and effects.* When antiprogestogens are given prior to ovulation, they disrupt the normal sequence of follicular maturation. Depending on the dose and timing of administration, the treatment can cause regression of the dominant follicle and initiate a new cycle of follicle development.[31] However, a low dose may only halt the maturation of the follicle for a short time and, as soon as the antiprogestogen's influence is over, the same follicle may either proceed to ovulation or remain unruptured until the end of the cycle. For example, a single 5 mg dose of mifepristone given when the leading follicle was 14 mm in diameter retarded the growth of the follicle for up to 36 hours.[32]

Data from two studies suggest that to exert a blocking effect on ovulation, the antiprogestogen has to be given before the onset of the luteinizing hormone surge; if the surge has already started, it may be too late to inhibit ovulation with an antiprogestogen.[33]

This effect on follicular growth may be a general property of compounds that interfere with progesterone receptor function. A recent study that investigated the effect on follicular growth of the antiprogesterone onapristone (administered in daily doses of 5 mg, 15 mg and 50 mg on days 5–11 of the cycle) found that the lowest dose affected follicular growth inconsistently, but that the two higher doses arrested both follicular growth and the preovulatory surge in estradiol, and also delayed the gonadotropin surge.[34] After treatment was discontinued, the leading follicle resumed its growth and ovulation occurred.

Studies conducted to determine whether mifepristone affects fertilization show that if ovulation occurs despite treatment, the ovum appears capable of fertilization. For example, in a study of the effect of mifepristone on in vitro fertilization of human oocytes, the researchers administered 100 mg orally 35 hours before recovering the oocytes through laparoscopy (when the follicular diameter was greater than 15 mm).[35] Although they found substantial amounts of mifepristone in follicular fluid, the in vitro fertilization and cleavage rates of the collected oocytes were not affected.

Whether mifepristone could influence the ability of spermatozoa to fertilize in vivo is unclear. Researchers have recently shown in vitro that high concentrations of mifepristone were required to slow sperm movement.[36] Such concentrations are unlikely to be reached in vivo in the tubal fluid.

Apart from affecting follicular maturation and ovulation (and possibly fertilization), mifepristone may prevent pregnancy by influencing the development and transport of embryos. Administration of mifepristone to rats accelerated embryo transport through the tube and caused the loss of embryos from the uterus before implantation. The treatment also delayed or arrested embryonic development.[37] Inhibition of the development of fertilized eggs by mifepristone has also been observed in other species.[38] Whether these mechanisms also contribute to the antifertility effects of mifepristone in the human is not known.

While treatment with mifepristone in the follicular phase inhibits follicle development, administration immediately after ovulation significantly affects endometrial maturation. For example, in one study, a 200 mg dose given in the evening of the second day after the luteinizing hormone peak delayed endometrial development for at least six days, even though circulating levels of progesterone were normal.[39] Similarly, onapristone had a strong inhibitory effect on endometrial development when administered on the second day after the luteinizing hormone peak.[40]

Furthermore, studies have shown that a single dose of mifepristone administered in the early luteal phase effectively prevented pregnancy in the rhesus monkey[41] and in humans.[42] In the latter study, 21 fertile women took 200 mg of mifepristone two days after the luteinizing hormone surge as their only method of contraception; only one pregnancy resulted during 157 cycles.

• *Efficacy of mifepristone.* Since mifepristone

disturbs several stages in the establishment of pregnancy, its promise as an emergency contraceptive led WHO to support two studies in the United Kingdom. Both studies compared the efficacy and side effects of 600 mg of mifepristone and the Yuzpe regimen when administered within 72 hours after unprotected intercourse.[43]

"Research on invasive tumor growth may provide some clues for the prevention of implantation—leads that could be exploited in future methods of emergency contraception."

The studies confirmed the potential value of antiprogestogens: There were no pregnancies among 597 women treated with mifepristone, while nine occurred among 589 women who received the Yuzpe regimen. In addition, the women who used mifepristone reported less nausea and vomiting and fewer other side effects than did those receiving the Yuzpe regimen. However, the women who took mifepristone were more likely than those receiving the Yuzpe regimen to experience a delay in the onset of menstruation (50% vs. 16%); this delay was presumably tied to the antiprogestogen's effect on follicular development and ovulation when it is taken in the preovulatory phase.

The 600 mg dose of mifepristone in the above studies is the same dose as that recommended for use with a prostaglandin to induce early abortion. Results from many studies on different aspects of the compound suggest that much lower doses may be effective in emergency contraception. For example, a dose as low as 5 mg arrested follicular maturation,[44] and a study examining the effects of 10 mg and 100 mg doses of mifepristone when given on day six and day 10 found similar declines in levels of both luteinizing hormone and follicle-stimulating hormone.[45] Further, a 10 mg dose administered prior to ovulation—when the follicular diameter is 18 mm or more—appears to block ovulation.[46]

The earlier during the secretory phase that mifepristone is administered, the more marked is its effect on the endometrium. An examination of different doses of mifepristone (ranging from 5 mg to 200 mg), taken from the second until the fifth day after the luteinizing hormone peak, found that the effects on secretory activity of endometrial glandular cells on any given day were essentially similar, irrespective of the dose.[47] Another study observed abnormal secretory maturation of the endometrium—considered to be incompatible with successful implantation—after two doses of 10 mg of mifepristone taken 72 hours apart on the fifth day and the eighth day after the luteinizing hormone surge.[48] A similar desynchronization of the endometrium occurred after 10 mg of mifepristone was given daily for four days starting on the day of ovulation.[49]

These studies suggest that mifepristone doses below 600 mg could be effective in emergency contraception. A WHO multicenter study currently under way will test this hypothesis by first confirming the effectiveness of the 600 mg dose and then assessing whether the same effectiveness can be achieved with lower doses—of 50 mg and 10 mg—and with longer intervals after unprotected coitus (up to 120 hours). The study will also evaluate side effects, including changes in the onset of the next menstrual period following use of the three antiprogestogen doses under examination. If this study should show that mifepristone is an effective emergency contraceptive in a dose that is much lower than that required for inducing early abortion, it may be possible to obtain marketing approval of the compound for an emergency contraception indication, even in countries that have restrictive abortion legislation.

Potential Research Directions

Scant information exists about the postfertilization events critical for successful establishment of pregnancy in the human. Research is in progress, however, in a number of areas, including embryonic development and signaling before implantation, tubal transport and milieu, endometrial development before implantation and the interrelationships between the embryo and the uterus during implantation. Each of these topics may provide leads to the development of more effective approaches to emergency contraception.

There is increasing evidence, for example, that the embryo plays an active role in the implantation process. Even before implantation, the human embryo produces a number of substances, including growth factors and hormones such as GnRH, human chorionic gonadotropin, estrogens and progesterone. Before implantation begins, an active exchange of messages is established between the embryo and the endometrium; signals such as early pregnancy factor, embryo-derived pregnancy-associated factor and human chorionic gonadotropin (in addition to signals yet to be discovered) might be candidates for targeting.[50]

These embryonic signals appear to be important in endometrial preparation for implantation. For instance, recent research in the rhesus monkey has shown that in the presence of a preimplantation blastocyst, luteal-phase endometrium differs morphologically from the comparable endometrial stage in nonfecund cycles.[51] Whether similar changes occur in the human is not known, but it is possible that the human endometrium may be morphologically and functionally different during conception cycles than during nonconception cycles. This should be taken into account when results from research into mechanisms of action of emergency contraception are interpreted.*

Since decidualization of the endometrium is obligatory if implantation is to occur, any compound that impairs this endometrial process is likely to interfere with implantation. Some research carried out in the context of in vitro fertilization also suggests that the developmental stage of the endometrium appears to be important for successful implantation: If endometrial development is "out of phase" (especially if it is delayed with regard to the developmental stage of the embryo), implantation is less likely to succeed.[52]

On the other hand, other evidence suggests that the window for implantation in the human is relatively wide, compared with that of laboratory animals.[53] The extent to which findings collected during the course of assisted conception apply to normal, fertile women is uncertain. As the human blastocyst is capable of implanting at extrauterine locations, there may not be rigorous requirements for nidation to succeed.

Despite the uncertainty about the need for close synchrony between the embryo and the endometrium, events in the endometrium around the time of implantation indicate that at least some preparation of the endometrium for nidation does take place, even in nonfecund cycles. The endometrial epithelium has a highly specific appearance: Microvilli, which are present after ovulation, disappear six days after

*Such research is by necessity done in women not exposed to the risk of pregnancy, and changes (or lack of changes) observed in, for example, the endometrium of these women following treatment with emergency contraception may not coincide with what would have been observed if a preimplantation embryo had been present.

ovulation; the cells are then covered with pyramidal protrusions called pinopodes, which disappear, in turn, nine days after ovulation.[54] The transient appearance of pinopodes corresponds to the presumed time of nidation. These protrusions apparently absorb uterine fluid and facilitate implantation by bringing blastocysts and the uterine epithelium into intimate contact, thus permitting adhesion.[55]

Specific binding proteins expressed while the embryo adheres to the endometrial epithelium may also offer a potential means of interfering with implantation. However, realization of this potential will require more detailed knowledge of the adhesion process in humans and the factors regulating it.

Toward the time of implantation, the number of large granular lymphocytes in the endometrium increases. It has been suggested that the products made by these cells control the process of the invasion of the endometrium by the implanting blastocyst.[56] In addition, other factors of potential interest include the leukemia inhibitory factor, which is expressed in the surface and glandular epithelium of the endometrium. This factor has been shown to be indispensable for implantation in the mouse. Without it, implantation cannot take place, even though embryonic development is normal and transferred embryos from mice deficient in this factor implant and develop normally in surrogate mothers.[57]

Leukemia inhibitory factor has also been identified in the human endometrium,[58] but whether this factor has the same importance in humans as in the mouse remains to be determined. Other substances, especially proteins produced by the endometrial stroma, are also of interest in this context, but their role in implantation remains unclear.

Finally, the high invasiveness of the human trophoblast resembles the behavior of malignant tissues. In addition, the interaction between the trophoblast and the uterus appears, immunologically, to be more akin to a tumor-host relationship than to a graft-host relationship. Thus, results from research on invasive tumor growth may also provide some clues on potential leads for the prevention of implantation—leads that could be exploited in future methods of emergency contraception.

Conclusions

This review of prospects for new approaches to emergency contraception suggests that basic research is unlikely to yield any new methods in the near future. Currently, the most pressing need is to develop antiprogestogens to serve as emergency postcoital methods. Mifepristone appears to have many advantages over the Yuzpe regimen, since it is easier to administer (only one dose is needed), is more effective and causes fewer side effects. In countries where an antiprogestogen-based method cannot be made available, levonorgestrel may prove a better option than the Yuzpe regimen, if further trials confirm its efficacy as an emergency method.

Antiprogestogens might also broaden the window of efficacy if they can extend the deadline for administration of the method. The ongoing WHO multicenter trial, for example, is examining whether mifepristone is effective up to five days after intercourse. This may be the outside limit of effectiveness, however, since several studies have concluded that an antiprogestogen alone is no longer very effective once implantation has started.[59]

Women who are given mifepristone should be informed of the possible delay in the onset of menstruation, since such a delay may cause anxiety and uncertainty about the treatment's success. Counseling women about the potential risk of conceiving later in the same cycle in case of further unprotected coitus is also important. The possibility of further unprotected intercourse should be taken into account when designing efficacy studies: If a woman becomes pregnant in the treatment cycle, it may not necessarily reflect a method failure. The study design should provide for the most accurate estimate of the timing of conception possible, preferably by ultrasound.

Women should also be warned about the possibility that the antiprogestogen may induce a vaginal bleeding episode within the first few days after taking the drug. Drug-induced bleeding is uncommon after treatment in the early luteal phase, but it may occur if the drug is taken in the middle of the luteal phase, and women need to be aware that it does not necessarily signify that the treatment has been successful.

Women should be in a position to benefit from new methods of emergency contraception that prevent unwanted pregnancies and avoid unnecessary abortions. Thus, as soon as researchers have established the lowest effective dose of mifepristone, this method of emergency contraception should be introduced into clinical practice, wherever this can be done.

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