



IPPF Medical Bulletin

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Emergency contraception pills: how do they work?

Horacio B Croxatto

The mode of action of emergency contraception (EC) has become the subject of heated debate in several countries. The main question centres on whether or not EC prevents pregnancy by interfering with post-fertilisation events. This issue is of importance for many people who believe that a new human life begins at the time fertilisation is completed; thus, interference with post-fertilisation events would lead to loss of human life.

Current EC pills contain 0.75 mg levonorgestrel (LNG) or 0.5 mg LNG plus 0.1 mg ethinylestradiol (Yuzpe regimen), and two doses must be taken 12 hours apart. When taken within 72 hours after intercourse, these pills are believed to prevent about 75% of the pregnancies that would have otherwise occurred.^{1,2} Research efforts to discover exactly how they prevent pregnancy, and why they fail more often than regular contraceptive pills, have been only partly successful.

The window for EC pills

There are only six fertile days in the menstrual cycle – that is, days in which an act of sexual intercourse can give rise to pregnancy. These are the day of ovulation and the five preceding days.³ Thus, in most cases spermatozoa have to wait one to five days in the female genital tract before encountering the ovum. This interval provides an opportunity to interfere with the migration and function of the sperm and/or with the process of ovulation. EC pills may prevent the encounter of spermatozoa with the ovum; and, even if the two gametes do come in contact, fertilisation may not proceed to completion.

Fertilisation in human beings is not very efficient: in ideal circumstances, when intercourse takes place during the most fertile days, the chance that fertilisation will take place does not exceed 50%;⁴ and it is plausible that even minor alterations in the preceding processes will greatly lessen the likelihood. This possibility has been explored experimentally in a few studies, and EC pills do interfere with pre-fertilisation events.⁵ But what if the pills are taken too late to prevent fertilisation? Two possibilities emerge – (a) that EC will not be effective and the method fails; (b) that EC prevents pregnancy, in which case it acts after fertilisation. When a woman uses EC, she does not know whether she takes the pills before or after ovulation, before or after fertilisation. For ethical and logistic reasons, it has not been possible to segregate groups of women who take EC after fertilisation so as to assess its effect on the establishment of pregnancy. Hence, there is no direct evidence either for or

against the hypothesis that EC pills prevent pregnancy by interference with post-fertilisation events.

Effects on the migration and function of spermatozoa

Administration of 400 µg LNG 3–10 hours after sexual intercourse affected sperm migration between 3 and 9 hours after treatment. It reduced the number of spermatozoa recovered from the uterine cavity, increased the pH of the uterine fluid (which immobilised spermatozoa), and increased the viscosity of cervical mucus (which impeded further passage of sperm cells into the uterine cavity).⁶ Although the investigators used only 57% of the current LNG dosage, these results are highly relevant to the actions of LNG used as an emergency contraceptive. There are no similar studies for the Yuzpe regimen.

The few data available indicate that, as in other mammals, sperm migration in women occurs in two phases.⁷ In the first phase, a few minutes after insemination some spermatozoa, aided by propulsive contractions of the genital tract, reach the fallopian tube. In the second phase, over several days, spermatozoa that have been stored in the crypts of the uterine cervix migrate in successive cohorts towards the fallopian tube. Only those from the second phase have the ability to fertilise. As spermatozoa reach the fallopian tube, many proceed to the peritoneal cavity. Non-capacitated spermatozoa attach themselves to the tubal epithelium for a few hours until they become capacitated, whereupon they become hypermotile and resume their journey. Once capacitated, spermatozoa do not remain viable for long; thus, to maintain a fertile population of spermatozoa continuously within the tube until the time of ovulation, it is essential that fresh cohorts keep migrating from the cervical reservoir. If ovulation occurs after a woman has taken LNG, interference with the sustained phase of sperm migration could well reduce or eliminate the probability of fertilisation.

Effects on the ovulatory process

Current understanding of the ovulatory process indicates that, when a normal gonadotropin surge acts on a mature follicle, it sets in motion a series of coordinated local responses that eventually lead to the extrusion of a fertilisable oocyte and the formation of a fully functional corpus luteum. These responses can be summarised as follows: resumption and completion of the first meiotic division; expansion of the cumulus oophorus and detachment of the cumulus-oocyte complex from the follicle wall; activation of a collagenolytic cascade; luteinisation of granulosa and theca cells; angiogenic invasion of the granulosa; and follicle rupture and voiding. Only the gonadotropin surge, follicular rupture, and functional luteinisation (as indicated by progesterone measurements) can be assessed in clinical studies without use of invasive methods. The coordinated development of these responses requires a normal gonadotropin surge and proper evolution of the ensuing signalling cascades inside the follicle; and, when this fails, the result can be ovulatory dysfunction^{8–13} and compromised fertilisation.^{14,15}

Several research groups, using diverse experimental designs, have explored the possibility that EC pills alter the

ovulatory process in women. All of them, without exception, have found instances in which none of the measured indices were abnormal as well as others in which either the luteinising hormone peak was partly or totally suppressed or postponed, or luteinisation failed partly or totally. The results seem to depend on the timing of EC administration relative to the ovarian cycle (see ref 5 for review). When the Yuzpe method was administered in the follicular phase, there was good correlation between follicular development at the time of treatment (leading follicle 12–14 mm, 15–17 mm, or ≥ 18 mm in diameter) and inhibition of follicular rupture followed by a rise in progesterone. Ovulation was prevented in 80%, 50%, and 0% of the cases, respectively, and ovulatory dysfunction was present in another 25% of the treated cycles.¹⁶ It is therefore plausible that lack of ovulation and ovulatory dysfunction account for the contraceptive effect in 90% of the cases who take the Yuzpe regimen when the leading follicle is 12–17 mm at the time of treatment.

Depending on how close to the luteinising hormone peak the treatment is given, LNG inhibits or postpones the gonadotropin surge or the rupture of the follicle, or interferes with the formation of the corpus luteum, or has no effect on the indices.^{17–19} Clearly, therefore, EC pills given during the follicular phase have the capacity to interfere with the ovulatory process, whether it be suppression of the LH peak, of follicular rupture, or of luteinisation.

Effects on the endometrium

The only post-fertilisation mechanism that has been investigated, and only indirectly, is an alteration in endometrial receptivity that could interfere with implantation. Endometrial biopsies have been obtained in women who took EC pills at about the time implantation would occur in a fertile cycle, and compared with similar biopsies taken during control cycles in the same women. Treated cycles in which the ovulatory process is believed to be abnormal or suppressed are excluded since endometrial development would reflect abnormal ovarian function rather than a direct effect of the EC pill. Some studies have found alterations in endometrial morphology or in the expression of certain progesterone-dependent molecules.^{20–22} Whether such changes have any impact on endometrial receptivity is open to question. Other workers have found either negligible alterations or none;^{18,19,23,24} and in the case of LNG existing evidence does not support the hypothesis that it alters endometrial receptivity or impedes implantation.

From a physiological and pharmacological point of view, the administration of synthetic progestogens such as LNG is highly unlikely to reduce endometrial receptivity. Progestogens, whether natural or synthetic, are so called because of their ability to *sustain* pregnancy in ovariectomised animals. The 25% failure rate of EC and the fact that it works best when used soon after sexual intercourse²⁵ are further reasons for doubting that this method impedes pregnancy by interference with post-fertilisation events.

Conclusion

The studies conducted so far have not fully characterised the mechanisms of action of EC pills. The information analysed provides evidence for pre-fertilisation effects and offers no evidence that EC pills prevent pregnancy by interfering with implantation of fertilised eggs.

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The decline in fertility with age

Alison Scott

With the recent pregnancies of several prominent women in their 40s, there has been much media interest in changes in fertility rates with age: “how late can you leave it before it’s too late?”. Thus a research paper by Dunson et al¹ attracted special attention. Some journalists interpreted the results as meaning that women should not delay having a family much beyond their late 20s.

Dunson and his co-workers reported on 782 European couples who kept daily records of the female partner’s body temperature, of when intercourse took place, and of menstrual bleeding. The women were stratified into four age groups, and the data allowed estimates of the chance of pregnancy on any given day of the cycle. Women aged 19–26 (with partners of the same age) had a 50% chance of conceiving in any one cycle, if intercourse took place at the peak time – ie, 2 days before ovulation. This fell to 40% in women aged 27–34 and < 30% at age 35–39. The authors’ conclusion was that “the probability of pregnancy declined for women from the late 20s onwards”. There is a male factor also: the fertility of men declined by the late 30s.

For a woman, the question of when to try to conceive is affected by social as well as physical factors. How best can we advise a woman who is worried about the effect of her age on her fertility, on a pregnancy, or on the fetus?

Fertility

Before Dunson’s paper, the general view was that age had little effect on pregnancy until the mid-30s, and for most women the fact that the decline in fertility begins 5–10 years earlier is still not of great concern. However, it will be important to those whose fertility is already at risk from factors such as endometriosis or fibroids. Another group who should be worried are those with a family history of early natural menopause, which seems to have a genetic element²; the end of spontaneous fertility cannot be predicted with any precision. Unfortunately, assisted reproduction techniques such as in-vitro fertilisation likewise tend to be less successful as the woman gets older. With women in their late 30s and early 40s, the ovaries become less responsive to synthetic follicle-stimulating hormone (used in assisted reproductive techniques), so ova may be unobtainable. But probably more important is the effect of age on the ovum itself. This is best shown by results with donor eggs: women over 40 have much higher pregnancy rates with ova from younger women than with their own eggs.³ In addition, it appears that better quality embryos are required to achieve a pregnancy in an ‘aging uterus’ than in younger women.⁴ The use of donor eggs may be an option for infertile women, but it raises difficult ethical, moral, and relationship issues for some couples. Another option now being explored is for young women to have eggs frozen and stored, for possible use later in life.

Miscarriage

Overall, about one in five pregnancies ends in miscarriage (spontaneous abortion). The largest cause of miscarriage in any woman is chromosomal abnormality of the conceptus, and the risk increases with the age of the oocyte. At age 40, for example, a woman’s risk of conceiving a baby with trisomy 21 (Down’s syndrome) is 1:84, compared with 1:1465 at the age of 20.⁵

Pregnancy complications

When a woman becomes pregnant past the age of 35, she becomes at increased risk of ectopic pregnancy, gestational hypertension, pre-eclampsia, and gestational diabetes. A woman aged 35–40 is 2.6 times more likely than a woman under 35 to get gestational diabetes, and in the over-40s the risk is even higher. Women over 35 are also at increased risk of operative vaginal delivery, elective caesarean section, and emergency caesarean section. An increased likelihood of stillbirth is attributed to fetal chromosomal anomalies and intrauterine growth restriction as well as maternal pre-eclampsia and diabetes.⁶

Education

A book by Sylvia Ann Hewlett, *Baby Hunger*,⁷ claims that thousands of career women are losing their chance of family by delaying childbirth. Childlessness had become a ‘creeping non-choice’; no-one, these women complained, had warned them. Seemingly many women, even some who are highly educated, are still unaware of the decline in fertility with age, and perhaps schools should be transmitting information on this matter along with advice on contraception. They may also have undue faith in in-vitro fertilisation: women of all ages tend to overestimate the success rates of assisted reproductive techniques – especially, perhaps, older women who are high achievers and not accustomed to failing a challenge. In view of the additional pregnancy risks previously mentioned, it is particularly important that older women take heed of general preconceptional advice regarding stopping smoking, taking exercise, reducing alcohol intake, taking folic acid supplements, and attending regularly for antenatal care with its options for fetal screening.

The picture is not all gloom. There are advantages to children from having mature parents. They tend to do well at school^{8,9} and will gain in other ways from the stability and accumulated wisdom of the relationship. Thus biological disadvantage may ultimately become social advantage.

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Essure: a new device for outpatient female sterilisation

Edith Weisberg

Female sterilisation is a popular choice for contraception in most countries. About 190 million couples throughout the world rely on female sterilisation for birth control.¹ Sterilisation is generally performed laparoscopically or through a minilap, depending on timing (postpartum or interval), the availability of surgeons with the necessary skills, and local resources. In western countries most of the procedures are performed under general anaesthesia, while in many developing countries the major method is minilap under local anaesthesia. However, despite the development of less invasive techniques, the risks, morbidity rates, and recovery time are still greater than for vasectomy.

There has been much interest in finding a non-surgical method of fallopian tube occlusion, achieved by insertion of a chemical or device through the cervix under local anaesthesia. Many chemical agents have been tried both in animals and in humans, including phenol based compounds, quinacrine, silicone plugs, and methylcyanoacrylate. None of these has proved satisfactory. Silicone plugs had an expulsion rate of 3.6–6.3% at three months.² Quinacrine was moderately effective³ but is a toxic substance which is no longer manufactured.

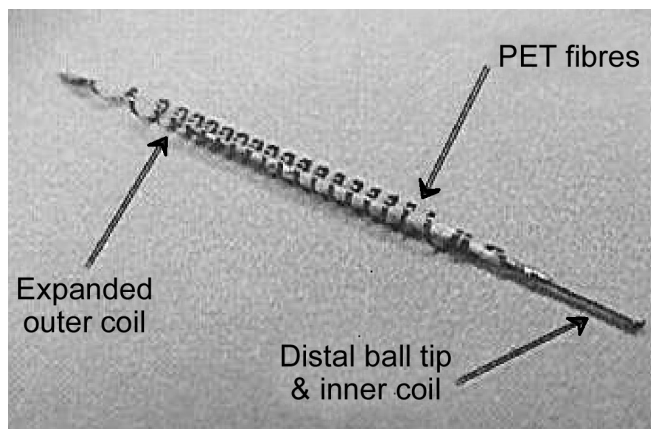
Essure

The Essure device consists of a central coil and PET fibres surrounded by an outer expanding superelastic Nitinol coil. The device is 4 cm long with a diameter of 0.8 mm which increases to 1.5–2 mm as the outer coil expands. The expanded outer coil anchors the device in the fallopian tube while the dacron polyester PET fibres encourage tissue reaction and long-term fixation. The device is attached to a delivery wire and inserted by means of a catheter through a hysteroscope into the proximal portion of the fallopian tube. The delivery wire is then detached, leaving the device in place with the outer coil spanning the uterotubal junction to enhance anchorage and with 5–10 mm intruding into the uterine cavity. The procedure is then repeated on the other side.

Following placement there is a benign localised tissue reaction, which over time produces full tubal occlusion. The response is confined to the area containing PET fibres, which become completely incorporated into the fallopian tube. The tissue reaction consists of an initial influx of inflammatory cells and giant cells in response to the presence of a foreign body. This is followed by growth of fibrous tissue and smooth-muscle fibres through the expanded outer coil, and by formation of blood vessels, resulting in full tubal occlusion. At the distal end of the device where no PET fibres exist, tubal architecture is normal; the tube is patent above the device. Occlusion is usually complete within three months of insertion. Women need to use alternative methods of contraception for the first three months. Initially hysterosalpingograms were performed at three months to demonstrate tubal occlusion, but experience with the device indicates that this is not necessary.

Advantages

The major advantages of Essure are that insertion is an outpatient procedure, conducted under local anaesthesia (cervical block) or with use of a short-acting intravenous tranquilliser, and requires no surgical incision. Although about two-thirds of women experience some pain during the procedure most report this as being less or equal to their expectation; pain tolerance is good to excellent in most women. Recovery time is rapid and women can return to normal duties on the day of insertion or the day after.



THE ESSURE DEVICE

Disadvantages

The major disadvantage of the method is that insertion requires considerable hysteroscopic skill, and careful training is necessary. The device is expensive and this plus the hysteroscopic skill required may make it unsuitable for many family planning programmes. Tubal occlusion with Essure is not reversible. Also, the devices cannot always be placed bilaterally, because of spasm or abnormalities of the tube. In the only published data Kerin et al⁴ reported that bilateral placement was achieved in 85% of women – a figure that may improve as inserters gain experience. If placement is unsatisfactory, the device may be expelled into the uterus.

Since this is a new device, there is so far no information on the effect of the protruding portion of the device into the uterine cavity if endometrial ablation is required or if the woman reverses her decision regarding further pregnancy and becomes pregnant after in-vitro fertilisation. Essure will not affect the functioning of magnetic resonance imaging machines.

Conclusion

Essure is the first female sterilisation technique that is comparable to vasectomy in respect of invasiveness, recovery time, and morbidity. As with vasectomy, other methods of contraception are required for the first three months, to allow full tubal occlusion to develop.

The major advantage of Essure is that it requires no surgical incision, can be inserted under local anaesthesia or a short-acting tranquilliser, and has a rapid recovery time. Most women are able to continue with their normal duties within a few hours after insertion.

Several factors militate against widespread use of the device. Successful placement requires an experienced and careful hysteroscopist with specialised training in the technique. The devices are also expensive.

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