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The Pill in new clothes



IPPH/MITEX-GOT INWALTER

Since its introduction in the late 1950s the Pill has become one of the most widely used and studied drugs in modern medicine. In this article, *Dr Roberto Rivera* of Family Health International reviews changes in its composition and presentation over the years.

Rwandan nurse preparing injection of Depo-Provera.

One particularly noticeable aspect of the Pill's evolution is how it has been losing weight throughout time. From its original composition to the current presentation there has been a progressive reduction in its contents; several milligrammes of hormone have become a fraction of that amount. The heavy Pill of the 1960s turned into the

light Pill of the 1980s. As commonly happens, the weight loss resulted in a healthier and safer Pill. It seems as if the Pill had been getting ready to wear its new clothes.

However, some practical problems remain with the Pill that are not related to the biological properties of the drug, but to the conditions of its use. To achieve the proper contraceptive effect of the Pill it is necessary to ensure correct and consistent use of the product, to swallow the Pill day after day, for as long as the contraception is desired. This is a difficult schedule to follow for many women and compliance is a problem for individuals and for family planning programmes.

How to make the Pill "easier to swallow" has been a worldwide concern. The new clothes of the Pill are so called delivery systems. The same active ingredients of the Pill are contained in different ingenious systems that facilitate the administration of the drug, making it easier to take, more difficult to forget. It also seems that the Pill in her new clothes is more accepted in certain cultures and social classes.

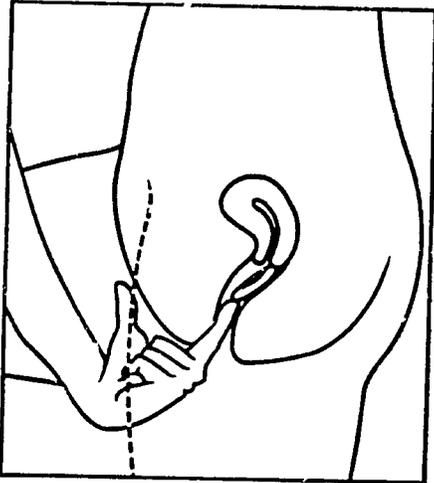
In the late 1960s it was shown that the daily administration of the progestational component of the Pill at a low-dose level was an effective means of contraception. This information was basic for the development of the new low-dose delivery systems. There are several contraceptive products of this kind already on the market, or in different stages of development, such as Norplant and other biodegradable or non-biodegradable implants, vaginal rings and biodegradable microspheres releasing different progestins. Two new kinds of monthly injectable are in a different category, but they have been used in extended clinical trials and one of them is already on the market in some countries.

The main advantages of the new long-acting methods are the ease of use and the high contraceptive effectiveness. The long duration, up to several years, of the contraceptive action is achieved after the initial application of the method, without the need of having to remember again how or when to use it. This long duration of contraception with a minimal effort is

Vaginal ring trial

Final trials are now under way to assess a manufactured version of the vaginal ring which will be launched later this year in Britain by Roussel-UK. The ring releases low doses of levonorgestrel, a progestagen hormone.

The hormone is contained inside the sterile ring and is released at the rate of 20 microgrammes over 24 hours. This is a much lower dose than the progestagen-only Pill, which contains 30 to 35 microgrammes of progestagen. The lower dose is possible because the vaginal ring is situated near the ovaries and the hormone does not have to pass through the liver as with oral contraceptives.



The IVR or intra-vaginal ring, as it will probably be known, is kept in place for 90 days after which it is replaced by a new one. The ring is easy to put in and can be taken out for short periods to be rinsed, or even during intercourse. It does not need to be fitted in place over the cervix as the diaphragm does, so there is only one size and no need for special fittings. Trials show the ring to be 96 to 99 per cent effective in preventing pregnancy – about the same as the progestagen-only Pill.

The IVR does have its problems: like all progestagen-only Pills or injectables it causes irregular bleeding in many women, and the

ring can also cause a vaginal discharge. A ring releasing both oestrogens and progestagens is currently on trial in 10 European countries; this ring is left in place for three weeks and then removed for a week's withdrawal bleed.

As with the Roussel ring, the hormones are delivered in much lower doses and do not pass through the liver, thus cutting down on side-effects. However, it will probably be five years before the 'combined' vaginal ring is generally available.

When vaginal rings are widely released, they will offer women another choice in contraception, and are likely to be welcomed by family planning workers worldwide.

Vivienne and Diane are two women who have taken part in the final three-month trial at the Hammersmith Hospital, London to assess the manufactured version of the progestagen-only ring. Vivienne is 30 and divorced with no children, but has a steady boyfriend. When first married she took the Pill for 8 years, but said she had now reached an age where she was uncertain about continuing to take relatively high doses of hormones. She works as a midwife and found out about the trial through colleagues at the hospital and thought the ring sounded a good idea.

"In fact, I'm disappointed," she said. "I don't like it. It's still a hormonal method, though a lower dose, and I'm not sure I'm happy about that. Then, while using it I've had periods every eight days lasting for about six days."

Vivienne says the ring is not hard to insert although it is larger and more rigid than a diaphragm or cap, and is easy to remove and replace. She says her boyfriend could feel it sometimes during intercourse (the ring can be removed for intercourse if the couple prefer). She also feels that she is retaining fluid, as she did on the Pill, and has put on weight.

"There are advantages; you can

put it in and forget about it unlike the cap, and don't have to remember to take it like the Pill. But for me the disadvantages outweigh that. In fact at the end of the trial I shall be very glad to take it out!"

Diane is 32, and while unmarried has been living with a steady partner. She came off the Pill because of concern about health risks and has used the cap for many years.

"I forget the ring is there most of the time," says Diane. "It seems to have improved my problems with pre-menstrual tension – my moods aren't so up and down, and I don't suffer from breast tenderness so much. I normally have a 26-day menstrual cycle – with the ring that's changed to 24 but it's regular, and I haven't had bleeding in between as some people have, and the bleeding hasn't been heavy. The main problem I've had is that if I use a tampon it's easy to pull the ring out with it – it can easily end up down the loo!"

"You can take it out easily, wash it and put it in again. You don't have to worry about getting it in right as you do with the cap. I've noticed that it increases my vaginal discharge, but this isn't excessive or irritating, though I suppose it must be possible to introduce an infection. My partner does sometimes feel it during intercourse but it doesn't really interfere."

Diane feels very positive about the method. "Although it is still hormonal, it's a lower dose than the Pill. It seems to suit me – I feel well, my PMT's improved and I've lost a bit of weight. It's so convenient and you don't have to worry about taking it or remembering to put it in.

"I did need reassurance that it wouldn't affect my chances of having a baby once I'd stopped using it, as we're planning to start a family soon. But I would certainly use it when it's on the market as my normal method of contraception." ● *Maggie Jones*

very advantageous for many women. Most of these products only contain the progestin as the active compound and are oestrogen free, which results in the absence of the undesirable effects associated to oestrogen use.

Also, the total dose of progestin received during the effective period of the long-acting methods is lower than the dose that would be received using the Pill for the same period.

However, there are also some

problems with the use of these new methods. The insertion of the implants requires a certain level of expertise and a health centre background. Their removal is in general more difficult than the insertion and requires a

higher degree of skills and experience. These conditions pose difficulties to users and programmes. The vaginal rings require manipulation of the genitalia, which poses problems in some cultures.

Most clinical studies have shown that the main problem associated with the use of these methods is the alteration of the menstrual cycle, namely in the form of irregular or prolonged bleeding and amenorrhoea. These menstrual problems account for the main reason for discontinuation of the method. In general, at the present time, the cost of the use of these methods is higher than for Pills.

Implants

Norplant - developed by the Population Council and marketed by a Finnish company - is the most advanced of the new long-acting steroidal methods, and the first to achieve large-scale use. It consists of six rubber capsules the size of matchsticks containing levonorgestrel, which are implanted on the inside of the woman's upper arm.

A single application provides effective contraception for five years and can be removed at any time. Norplant is the most effective reversible contraceptive developed to date. Its contraceptive effect is due to ovulation inhibition and changes in the cervical mucus and the endometrium. One drawback is that insertion and removal require specific training and skills. The only problems have been with menstrual irregularities.

Norplant has already been approved for use in 14 countries. Approval by the US Food and Drug Administration is expected this year.

Annuelle, a biodegradable implant, is being tested by Family Health International (FHI). With this method, a pellet about the size of a grain of rice is inserted in the upper arm in a single application. It then releases norethisterone for one year. Because it is biodegradable, it does not require removal. Like Norplant, the main problems have been with alterations in the menstrual cycle and implantation requires specific training and skills. An improved formulation of this implant will soon be tested in extended clinical trials.

Another implant that releases levonorgestrel is in the early phase of clinical trials. Commonly called Capronor, it involves a single biodegradable capsule with a duration of one to two years.

Injectables

WHO's Human Reproduction Programme (WHO-HRP) has been active in the development of a steroidal contraceptive that involves a monthly injection. There are two variations: 25 mg of depot-medroxyprogesterone acetate with 5 mg of oestradiol cypionate, and 50 mg of norethisterone oenanthate with 5 mg of oestradiol valerate. Both have been used in extended multi-centred trials worldwide.

These injectables work mainly by inhibiting ovulation. Although the use of oestrogen helps to regulate the menstrual cycle, there is still some irregular bleeding.

Vaginal rings

Several vaginal rings are being developed. Their appearance has been delayed by concern some years ago about a catalyst used in the elastomer carrier. The elastomer manufacturer, Dow-Corning, withdrew the product while these concerns, which also affected the development of Norplant-2, a two-capsule implant, were investigated.

In the end they proved groundless, and one vaginal ring, manufactured by Roussel UK, has completed trials and will be launched in Britain as soon as it receives a product licence, probably before the end of this year. This ring delivers 20 microgrammes of levonorgestrel and is intended to stay in place for three months (see box). Another, being developed by the Population Council, releases both levonorgestrel or other progestogens, and estradiol. It is designed to remain in the vagina for three weeks and then be removed for one week to allow bleeding.

Microspheres

Made from biodegradable non-toxic polymers, these very tiny particles contain steroids and are administered by means of an intramuscular injection. As the microspheres biodegrade, the active steroid is released into the blood at a constant level for established periods of time.

The most advanced microspheres to date, which are being developed by Family Health International, are designed to deliver norethisterone for a 90-day period. The main drawbacks so far are irregular bleeding and amenorrhoea.

The Pill has come a long way in 30 years. Perhaps its new shapes and sizes will make contraception in the 1990s more attractive than ever.