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New developments in contraceptive technology

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Abstract

The demand for fertility control is expected to increase in the next two to three decades as the number of couples in the reproductive age groups in developing countries alone is expected to grow to nearly 1 billion. The crucial issues in the future will therefore be aimed at optimizing the use of currently available methods and making them safe, effective and acceptable, with minor alterations in composition or delivery system. In addition, there should be new developments in contraceptive technology.

In this paper, an update will be given of the work presently underway on improving existing methods of fertility control and also on the research being undertaken on possible new contraceptive methods.

It is extremely difficult to predict with certainty the future direction of contraceptive technology. Workers and 'seers' in the field of contraceptive research predict no completely novel breakthrough in this century at least. Yet there is hope for some novel breakthrough in contraceptive technology from the work which is being done at present by independent researchers. Perhaps, these may bear fruit in the twenty-first century.

Introduction

The demand for fertility control is expected to increase in the next two to three decades as the number of couples in the reproductive age groups in developing countries alone is expected to grow to nearly 1 billion. The crucial issues in the future will therefore be aimed at optimizing the use of currently available methods and making them safe, effective and acceptable, with minor alterations in composition or delivery system. In addition, there is hope for some novel breakthrough in contraceptive technology from the work which is being done at present by independent researchers. Perhaps these may bear fruit in the twenty-first century.

This paper is based on a presentation given at the Seventh International Meeting of the Scoiety for the Advancement of Contraception, which was held in Singapore on 4–11 November, 1990.

In this paper, an update will be given of the work presently underway on improving existing methods of fertility control and also on the research being undertaken on possible new contraceptive methods.

Modifications of currently available methods

Oral contraceptives

Since its marketing in 1959, the combined oral contraceptive pill has proven to be popular and it is estimated that roughly 120 million women are on the 'pill' worldwide. In 1969, the estrogenic component of the pill was implicated as the thromboembolism associated with the pill [1]. Subsequently, the Royal College of General Practitioners study in 1977 implicated the progestogens in the oral pills for some of the adverse effects associated with their use [2]. Since then, it has come to be appreciated that, not only are doses of the estrogens and progestogens in the combined pill a determinant of cardiovascular disease potential, but so also is the combination or ratio of estrogen/progestogen [3–5]. Thus the main areas of research with oral contraceptives have been on modifications to enhance safety and at improving patient compliance and acceptability.

Modifications of the combined oral contraceptive pill to reduce complications can be classified into:

a) Modifications in the estrogen component;
b) Modifications in the progestogen component;
c) Slow-release formulations;
d) Strategies to improve compliance, acceptability and safety.

Modification in the estrogen component

Changes in estrogen

The original estrogen in the pill, mestranol, has been changed to ethinyl estradiol in most OCs to improve safety. It is now known that mestranol has to be converted to ethinyl estradiol in the body before it is active. Thus the change is a step in the right direction.

Reduced estrogen dosage

Reduction in estrogen dosage has brought with it a concomitant reduction of venous thrombosis. In 1968, 30% of all OCs contained more than 50 μg of estrogen but today this figure is less than 5% [6]. Currently, the 'micropill' containing 30 μg of estrogen is widely prescribed. This is probably as low as we can go with currently available

technology as attempts to introduce the 20 μg estrogen pill ran into the problems of poor cycle control and breakthrough bleeding [7].

Natural estrogens

The thrombogenic effects of the OC pill are due to the synthetic estrogens that it contains. Replacing ethinyl estradiol with naturally occurring estrogens (e.g. estrone, estradiol) would result in less cardiovascular and metabolic upsets. However, initial experience with natural estrogens has been disappointing with gastrointestinal and menstrual upsets being the chief problems [8].

Modifications in the progestogen component

The aim is to develop a progestogen that has minimal or no metabolic effects (and thus minimize atheromatous and metabolic complications) when given together with conventional low doses of ethinyl estradiol. The changes in the progestogen components over the years can be classified as follows.

Reduced progestogen dosage

Since it is now realized that the progestogens may be more important in the etiology of atherosclerosis and myocardial infarction, the trend over the years has been to lower the dosage of progestogens. Indeed, currently, lower doses of the three original progestogens – norethynodrel, norethisterone and lynestrenol – are being used.

In addition, there is the quantitative approach to reduce the overall intake of progestogens per cycle of use, for example, a commonly available triphasic (Triquilar) loads women with 1925 μg/month norgestrel compared with 3150 μg/month with the usual monophasic preparations (150 μg/pill as in Microgynon 30). This drastic reduction has been achieved without sacrificing efficacy. Although there is insufficient evidence to prove that the total steroid content of any given cycle is as important as the daily amount, it seems logical that any method that lowers the total amount of steroid ingested would be a positive step toward further reduction of complications and side-effects.

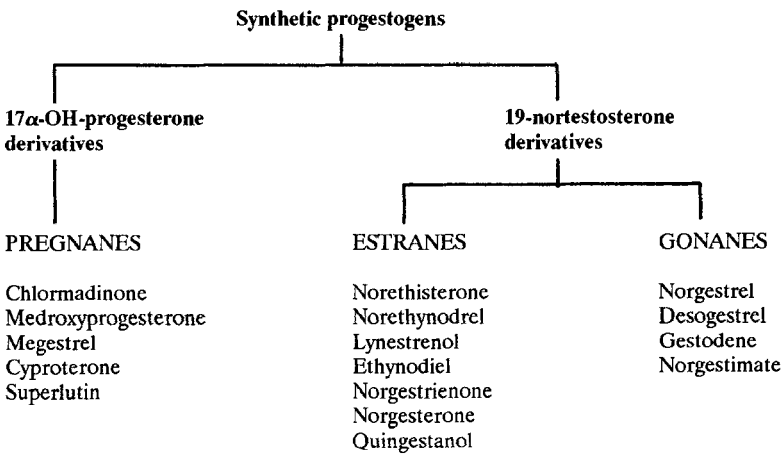
Newer progestogens

There seems to be an affinity between some progestogens and androgenic receptors and it is felt that this promotes the metabolic side-effects of the combined pill. Androgenic progestogens cause decreased sex hormone binding globulin and high-density lipoprotein level, the latter being an important determinant of arterial vascular disease. The androgenic activity of progestogens depends on its chemical

structure and this structure–activity relationship will determine which progestogen is the best one to use in the combined oral contraceptive pill.

All synthetic progestogens are derivatives of either 17α-hydroxyprogesterone or 19-nortestosterone (Table 1). The pregnanes (17α-OH-progesterone derivatives) are purely progestational and devoid of androgenic activity. They have a lower potential for impairing carbohydrate and lipid metabolism. However, since a little androgenic activity is required for better cycle control, pregnanes (except for cyproterone acetate) are seldom favored for use in the combined pill. The 19-nortestosterone derivatives are characterized according to their structure into the estranes and the biologically more effective gonanes. The estranes (e.g. norethisterone) are chemically characterized by the absence of a methyl group between rings A and B and by an ethinyl group in position 17α; these substitutions delay the compounds inactivation by the liver and greatly reduce the androgenic effects [9]. The gonanes share the structural features of estranes but, in addition, are characterized by an ethyl group in position 13 [9]. Among the gonanes are the most effective new synthetic progestogens, such as levonorgestrel, desogestrel, norgestimate and gestodene.

Table 1 Oral contraceptive progestogens



Research is therefore directed at finding a progestogen of strong activity (hence a gonane) with least androgenic activity (hence, one causing least metabolic upset). Therein lies the contentious issue regarding which of the new progestogens is more active, while causing the least upset in carbohydrate and lipoprotein metabolism. The important differences between the new progestogens and their influence on carbohydrate and lipid metabolism are shown in Tables 2, 3 and 4.

Table 2 Effects of various synthetic progestogens (Ref. 9)

Parameter	*Norethisterone*	*Levonorgestrel*	*Desogestrel*	*Norgestimate*	*Gestodene*
Ovulation inhibition (mg/day)	0.5	0.5 – 0.1	0.06	0.25	0.04
Transformation dosage (mg/cycle)	100 – 150	5 – 6	0.4 – 2.5	5 – 10	2 – 3
Menstrual delay test (mg/day)	10 – 15	0.25 – 1.0	0.25	5	0.2
Binding affinity to progesterone receptor	305	628	11	400 – 500	?
Maintenance of pregnancy	+	+	+	+	+
Estrogenic effects	+	0	0	0	0
Antiestrogenic effects	+	+	+	+	+
Androgenic effects	+	+	+	+	+
Antiandrogenic effects	0	0	0	0	0

Table 3 Influence of new monophasic pills on carbohydrate metabolism (Ref. 9)

		Glucose tolerance test	
Progestogen	*Combination*	*Glucose*	*Insulin*
Levonorgestrel	30 μg EE 150 μg LNG	Normal to slight increase for all preparations	Increased levels seen with all preparations
Desogestrel	30 μg EE 150 μg DSG		
Norgestimate	35 μg EE 250 μg NG		
Gestodene	30 μg EE 75 μg GTD		

EE = ethinyl estradiol; NG = norgestimate; GTD = gestodene; LNG = levonorgestrel; DSG = desogestrel

Table 4 Influence of monophasic pills on lipid metabolism (Ref. 9)

Progestogen	*Triglyceride*	*Total cholesterol*	*HDL cholesterol*
Levonorgestrel (30 μg EE, 150 μg LNG)	0 – 20% increase	Normal range for all preparations	Normal range Normal to slight ↑ Normal to slight ↑
Desogestrel (30 μg EE, 150 μg DSG)	0 – 20% increase		Normal range
Norgestimate (30 μg EE, 250 μg NG)	20 – 50% increase		
Gestodene (30 μg EE, 75 μg GTD)	20 – 30% increase		

EE = ethinyl estradiol; LNG = levonorgestrel; DSG = desogestrel; NG = norgestimate; GTD = gestodene

Slow-release formulations

Formulations which release steroids at a slow sustained constant rate when taken orally, could revolutionize the field of oral contraception as this would enable the use of lower doses of steroid. With this end in view, research in the development of microspheres and other formulations is underway [8]. If successful, they would ensure

even absorption of steroid with constant blood levels maintained over a 24-hour period. With such a formulation, perhaps the estrogen component of the pill could be lowered to 20 μg or less whilst maintaining cycle control and contraceptive efficacy.

Strategies to improve compliance, acceptability and safety

Whatever the results of laboratory testing and subsequent improvements may be, the final analysis of success depends on results from field testing. User failure, poor compliance and discontinuation rates have plagued many 'pill' programs. The frequency of such constraints varies not only from country to country but even between two clinics in the same country, as WHO trials have shown. Since no two populations are alike, research in the form of health service research and controlled clinical trials will be continued to assess the types of pill most suitable for particular groups of women.

Research has shown that more attractive packaging with easy-to-follow instructions may improve compliance in some cases. In others, a completely different formulation may be required. The paper pill formulation, for example, was shown to enhance compliance in a WHO study on 1400 women over 1000 woman-years of use when compared with the regular oral contraceptive pill [7].

Mode of administration of the pill is also being researched. To reduce the first pass effect on the liver (and thus reduce the metabolic consequences of oral contraceptives) oral contraceptives are being administered vaginally. The problem with the vaginal route is that absorption is not constant.

Injectables

The two currently used long-acting injectables are depomedroxyprogesterone acetate (DMPA) and norethisterone enanthate (NET-EN); a single injection is active for 3 and 2 monthly respectively [10]. Irregular bleeding, amenorrhea, possible slow return of fertility and effect on carbohydrate and lipid metabolism are some of the main side-effects associated with their use [11,12]. The menstrual disturbances are probably related to the fact that the currently available drugs are not released uniformly from the depot site – the drugs are initially released as a burst after injection reaching high levels which decline slowly until 4 weeks after injection [13]. However, despite all this, the number of users of injectables have doubled since 1981. Currently it is estimated that more than 6 million women are using injectable steroid formulations all over the world because of their convenience of use. Since the need is evident, research has been aimed at improving the injectables. Some of the approaches currently under investigation with this aim are to:

a) Develop newer steroids with better release profiles

WHO has sponsored a large-scale program for the synthesis of newer steroids

with better or zero-order release-rate profiles [14]. Four such esters of levonorgestrel have already been synthesized and toxicology studies have been started with the most promising compound, 22cc. Hall has reported promising work with esters of levonorgestrel which may have a 3–4 months duration of effect when given in doses as low as 10–20 mg.

b) *Increase the number of injections using smaller doses of existing steroids*

This has proved successful with low incidence of side-effects [15]. Moreover Prasad *et al.* [16] showed that there was consistent suppression of ovulation with the use of 20 mg of norethisterone enanthate monthly.

c) *Combine injectables with natural estrogens*

Combinations of cycloprovera (25 mg medroxyprogesterone acetate plus 5 mg estradiol cypionate) and a WHO compound, HRP 102 (NET-EN 50 mg plus 5 mg estradiol valerate), are under test and studies show little differences in efficacy and side-effects between the two formulations. However, one of the major objectives of adding estrogens to either progesterone preparation was to achieve a better control of vaginal bleeding. While it is acknowledged that they do not have a 'normal' menstrual bleeding episode, but rather, an estradiol withdrawal bleeding [17], it is nevertheless predictable and follows a specific bleeding-free interval, something not observed with any other long-acting hormonal contraception. This apparent normalization of vaginal bleeding patterns gave rise to a significant decrease in the discontinuation rates for bleeding irregularities and amenorrhea compared with the use of progestogen-alone injectables [18].

d) *Use new delivery systems to improve release characteristics*

This involves the delivery of the steroids in a small biodegradable polymer envelope or support matrix in the form of microcapsules or microspheres. The Family Health International has recently begun Phase III clinical trials on this new injectable contraceptive (called the norethindrone 90-day injectable microspheres). The injectable form of norethindrone is composed of microscopic time-release particles that keep the drug in the blood stream for 90 days. No serious side-effects have been observed to date. This approach may provide better release characteristics but it may prove difficult to obtain reproducible batches of the polymer. Problems may also be encountered with packaging; hence it is probable that the costs will be higher than for other injectables.

Steroid implants

Steroid implants, like injectables, are depot contraceptives, but, like depot injectables, they have a longer duration of action and have generally better release profiles.

Currently, both biodegradable and non-biodegradable implants are under development and review.

The Population Council with the approval of WHO, has continued with the introduction of Norplant in many countries throughout the world [19,20]. Norplant consists of 6 silicone capsules containing levonorgestrel and there is a sustained slow release of levonorgestrel for at least 5 years. The results to date have been promising [21,22]. In fact, in the interests of development and making Norplant more acceptable, a second-generation system, Norplant-2 rods, have been introduced and this new system is currently undergoing clinical trials in several countries. Norplant-2 rods consist of only 2 rods in which levonorgestrel is homogeneously dispersed and covered by a layer of Silastic. Results to date with its use have also been encouraging [22,23]. However, a recent setback has been that the medical-grade elastomer 382 used in the Norplant-2 rods was suspected to have a carcinogenic potential in rodents in a dose many thousand times greater than that used in Norplant-2. Because of this, there has been a withdrawal of medical-grade elastomer 382. More recently, the status of Norplant-2 rods has been reviewed by the USA Food and Drug Administration. The conclusion was that ongoing studies should continue while major efforts are being undertaken to investigate alternative elastomers to find a replacement for medical-grade elastomer 382 as soon as possible [24].

Research into non-Silastic biodegradable implants have proven clinically unsatisfactory although they are good biodegradable compounds with zero-order release [12,25]. Alzamer caused unacceptable local irritation, and caproner degraded twice as slowly as the rate at which the steroid (levonorgestrel) was released. Nevertheless, Caproner is still being developed and investigated. The Caproner implantable device consists of a poly(E-caprolactone) tube which contains levonorgestrel in an ethyl oleate vehicle. It is a single implant system which is expected to deliver levonorgestrel at a zero-order release rate for up to 2 years and which biodegrades after its steroid content is exhausted. It can be removed, if necessary, during the first few months after insertion. No local skin reactions have been observed during the use of this device [26].

In addition, recently Family Health International has been assessing the effectiveness of biodegradable norethindrone pellet implants. Norethindrone (NET) pellet implants are composed of 85% norethindrone and 15% cholesterol compressed and heated in an automated process to form pellets the size of a grain of rice. Four pellets implanted subdermally are expected to release NET over 12–18 months and are totally biodegradable within approximately 24 months. Phase I and phase II clinical trials have to date shown no pregnancy or safety problems, except for some menstrual disturbances – a side-effect common to the use of all progestogen-only agents for contraception.

Vaginal rings

Medicated vaginal rings with either spermicides or steroids are being developed. Two types of steroid vaginal rings are currently under review. The Population Council in

1972 began the development of a ring which released levonorgestrel and 17β-estradiol at a rate which inhibits ovulation [27]. This ring is designed to be worn for 3 weeks and is then removed for one week to induce withdrawal bleeding. Although development of this particular product has now been terminated because of estrogen-related adverse effects, other steroids and combinations of steroids are at present being investigated. WHO, on the other hand, has developed a vaginal ring, Varvelo 20, which releases a low dose of levonorgestrel only. Thus, it would not rely solely on the inhibition of ovulation, which occurs in about half of the subjects using the device, but also involves local effects on cervical mucus and endometrium. This ring is designed to be worn continuously. A recent set back in its development has been that the medical-grade elastomer 382 that is used to make the vaginal ring has been implicated with possible carcinogenic effects in rodents (see under *Steroid implants*). Thus, until alternative elastomers are found, further production and evaluation has been discontinued. However, the several advantages offered, namely that the device can be inserted, removed and replaced by the user herself without the need for medical or paramedical personnel, early checking if the device is still *in situ*, there is a constant release rate of drugs resulting in steady plasma levels and that the vaginal absorption of the steroid, avoiding the 'first-pass' effect on the liver, results in the drug reaching the target organ without having entered the enterohepatic circulation, make all the more necessary to persevere with the rings [28,29].

Improved IUDs

IUDs have been available for years. The major problems with IUDs relate to menstrual side-effects and hence high discontinuation rates. Currently, new IUDs have been designed to combat these problems in the hope of improving patient compliance in the future.

Generally, contraceptive efficacy and lifespan of IUDs has improved with the Copper T380A, T220C and the Multiload 375. Multicenter comparative clinical trials are now underway to compare these three devices with respect to whether or not the Multiload, which is currently more expensive than the three, offers any major advantage over the other copper devices.

Progesterone-containing IUDs were made in the hope of combating the heavy bleeding seen in IUD users. WHO introduced a levonorgestrel device that released 2 μg/24 hours. However, the use of this device has been discontinued since 1985 because of an unacceptably high incidence of ectopic pregnancy [30]. The Population Council has also introduced a 20 μg levonorgestrel-releasing IUD. This latter device has given pregnancy rates of 0.1–0.3 pregnancies per 100 women in the first year and is not associated with an increased pregnancy rate [31]. It also halves the preinsertion menstrual blood loss and improves dysmenorrhea. However, in 1987, it became apparent that this IUD would not be available for some time now because the medical elastomer 382 used in the manufacture of the hormone-releasing reservoir in this device has been shown to cause liver cancer in rodents (see under *Steroid implants*) [24]. Thus, until further toxicology tests are undertaken or an alternative

manufacturer may be found, no new trials are being undertaken over the next few years although the previously inserted devices are not being withdrawn.

Theoretically, the increased bleeding and pain experienced by some IUD users is associated with the size of the plastic skeleton which supports the copper wire. The Cu-Fix, which is to be tested soon in a multicentric trial against the TCU380A, has no frame but is simply a chain of copper cylinders hanging on a nylon thread from the fundus of the uterus. In order to place the thread, it is necessary to deliberately push the insertion needle into the myometrium and it has not been established how safe this procedure would be outside the hands of the device developer [31]. The Multiload mark 2 is yet another new device currently undergoing international trials with a radically new insertion system. The device itself has barium in the arms and is easier to remove than earlier versions [32].

The addition of various other bioactive substances using fibres has also been proposed for some time but it has, in general, proved impossible to store enough of the active principal to allow slow release over several years. Thus, devices releasing antiprostaglandins or antifibrinolytics have not proved practical [33]. The one exception may prove to be antiseptics, such as chlorhexidine, which could be contained in devices or tails to offer protection in the period immediately following insertion.

Improved barrier methods and spermicides

Besides the development of the female condom in the near future, it seems unlikely that any novel improvement is going to emerge as far as the other barrier methods are concerned. Studies undertaken for a vaginal collagen sponge have been disappointing in terms of patient compliance [34].

Nonoxynol 9 and TS88 have been the time-honored spermicides in current use. They are generally safe but may cause vaginal irritations. In addition to their safe use as foams, aerosols etc., they may also be impregnated in collagen sponges and vaginal rings [34].

Better methods of natural family planning

Natural family planning methods have in general been associated with high failure rates [35]. However, some women have no choice but to use them because of religious restrictions. Natural family planning methods depend heavily on methods attempting to predict or detect the occurrence of ovulation. A large number of potential indices of the fertile period (e.g. enzymes and steroids in saliva, vaginal secretions and urine, changes in temperature) have been critically assessed [36]. These studies reveal that the measurement of urinary luteinizing hormone (LH) [37] or of estrogen and progesterone metabolites [38] appear to be the best suited for the prediction and/or detection of ovulation. The ratio of the two best indices – urinary estrone glucuronide – and pregnanediol-3 glucuronide – seems to provide a 3–5 day warning of impending

ovulation [39]. Moreover, a well-defined rise in luteinizing hormone seems to be an indirect indication of impending ovulation, the median interval between the LH rise and ovulation being 32 hours [40]. WHO is therefore considering and developing a simple kit method for measurement of these metabolites and Gould and Faulkner [41] have described a rapid haemagglutination urine test for detecting the mid-cycle LH peak.

Improved basal body temperature measurement may be easily obtained in the future with the testing of the first automatic electric thermometers for clinical use [42]. These devices signal the start of the infertile phase of the cycle when the temperature has risen for 3 consecutive days.

More recently it has been suggested that the amount of cervicovaginal fluid increases during the follicular phase of the cycle and could be measured reliably and easily by women themselves on a daily basis using a calibrated disposable plastic aspirator [43]. This quantitative method may be a more suitable and effective approach to detecting the beginning and end of the fertile period than the somewhat subjective assessment of the cyclic changes of mucous secretions by self-observation methods. To test this hypothesis, investigations have been undertaken to determine the temporal relationship between volumetric aspiration data and fertility indices used in the symptothermal method of natural family planning.

Postcoital contraception

Estrogen in higher doses, estrogen/progestogen combinations and IUDs are effective methods of postcoital contraception for emergency use [44]. The hormonal methods have, in general, caused gastrointestinal upsets or menstrual irregularities [45]. Moreover, the high doses of estrogen required makes the use of postcoital estrogen unsuitable as an on-going contraceptive method. Postcoital progestins, on the other hand, seem to fit the bill as on-going contraceptives. Results of a WHO multicentre trial using 0.75 mg of levonorgestrel indicate it to be of value to certain women, such as those needing contraception for a short period only and/or having infrequent intercourse [46,47]. The failure rates per treated cycle observed in the studies suggest that this may be an effective alternative to high-dose estrogen or estrogen/progestogen combinations for use in emergency situations. However, it must be stressed that repeated postcoital use of levonorgestrel does not represent a viable approach to fertility regulation for the majority of women of reproductive age who have regular intercourse and who wish to limit the number of their pregnancies. For such women, the total drug load per cycle using this approach would be greater than that which occurs during the use of a progestogen-only pill. Furthermore, the incidence of cyclic disturbances resulting from levonorgestrel use might be higher than that encountered with other forms of progestogen-only contraception because of the irregular intermittent use of the drug.

In China, studies on other potential progestogens (in case levonorgestrel should not prove suitable for large-scale clinical use) have been carried out. Norethisterone (5 mg) has been used as a vacation pill for more than ten years in China and has

shown high efficacy (99.5%) with few side-effects [48]. Compared with levonorgestrel, norethisterone has the advantage that it forms tetrahydroderivatives with estrogenic activity which might have a beneficial effect by reducing the incidence of bleeding irregularities [49]. Recently, Song *et al.* [50] have shown that ovulation is suppressed as effectively with a 3 mg norethisterone-containing pill as with the 5 mg formulation currently in use. This finding, together with the results from a confirmatory clinical efficacy trial, may lead to a reduction in the hormone content of currently used pills.

Sterilization

Surgical female sterilization has currently become so simplified that it is unlikely to be superceded by any surgical innovation in the near future. The advances in this field are likely to be in the following areas:

Reversible female sterilization

The amenability to recanalization will depend on the primary method of tubal occlusion used. Fimbriectomy, extensive elective cautery and salpingectomy are irreversible. The use of clips, carbon dioxide lasers and ligation procedures causing limited tubal damage will allow for successful recanalization. However, up to the present, recanalization surgery needs special expertise with expensive microsurgical technique for an acceptably high success rate.

Recently, there have been some attempts to develop reversible methods of sterilization. The use of Silastic caps to contain either the fimbrial end (fimbriotexy) or ovary (ovariotexy) have been described. Intratubal plugs have also been tried but they are difficult to place in the tube and also difficult to remove; surgery being required both times. These plugs have also caused tissue irritation. They are therefore unlikely to be of much use in the future.

Non-surgical methods of sterilization

A variety of chemicals have been examined for their ability to cause tubal occlusion when instilled either blindly or under hysteroscopic control. Currently, quinacrine, methylcyanoacrylate (MCA) and Silastics appear promising. Quinacrine is better than MCA and Silastic in that it does not require any special device for instillation. However, its application has to be repeated to achieve bilateral occlusion [51]. MCA is a liquid monomer which polymerizes when in contact with moist living tissues. It then promotes fibrosis by releasing toxic products as it degrades over 6 weeks. Irreversibility is a disadvantage with this method [52]. Silastic has the potential of reversibility. This fast-setting substance has to be delivered hysteroscopically and 86% success rate has been reported [52].

However, all in all, it seems unlikely that these methods would be incorporated into family planning programs in less developed countries because of the expertise required.

New approaches for the future

Research in the field of family planning have been looking to several new leads. These are, however, in their infantile stage and may only become reality in the next century. Some possible and promising leads are:

a) LRF analogues for contraception and luteolysis

More than 1500 analogues of luteinizing release factor on hormone have been made and, according to their activity, have been deemed agonists or antagonists. When used in laboratory animals, agonists can be stimulatory or inhibitory depending on the species used.

LRF agonists have been investigated for female contraception from two angles – as ovulation inhibitors and as luteolytic agents. Their action to inhibit ovulation seems more promising than their luteolytic capability. Buserelin [D-Ser(TBu)^{6},desGly^{10}]-LRFS via the nasal and subcutaneous route, has been used for ovulation inhibition [53–55]. The results were acceptable with return of ovulation on cessation of LRF agonist. However, amenorrhea was a problem with this treatment and some have also suggested the possible side-effect of unopposed estrogenic action on the endometrium resulting from this treatment [56]. The use of LRF analogues for luteolysis is not so promising. When they were given to non-pregnant women, there occurred some shortening of the menstrual cycle [57] but this effect could not be duplicated in pregnant women [58].

LRF antagonists have been less well investigated than agonists because only recently have potent ones been available. Inhibition of ovulation has not been consistent in animal studies [59]. Further testing is necessary before any prediction can be made for LRF antagonists.

b) Various peptides for contraception

Many of the constituents in follicular fluid could prevent ovulation. If these peptides could be purified, they could provide very potent antiovulation agents which act directly on the target organ (Graffian follicle) and which will have none of the complications of steroidal contraceptives. Follicular inhibin [60], oocyte maturation inhibitor [61] and FSH binding inhibitor [62] are some of the novel peptides that may show future promise.

c) Plants for fertility regulation

Research has been going on to identify novel drug prototypes in plants alleged to have fertility regulating properties. In particular, compounds are being sought that are orally active, non-steroidal, non-estrogenic and will safely and effectively prevent or disrupt implantation or cause early abortifacient activity in women or which will inhibit spermatogenesis or interfere with sperm maturation in men. To date, nearly 400 plants have been evaluated in 6 countries and approximately 20% of these plants have been found to exhibit antifertility but not always of the type being sought.

The work that has reached the most advanced stage involves the plant, *Murraya Paniculata* [63]. A potent anti-implantation agent, Yuehchukene, has been isolated from this plant and is currently undergoing studies in marmosets to evaluate the anti-implantation potential. In Shanghai, a pure compound, pseudolaric acid B, isolated from *Pseudolarix kaempferi* appears to be maximally effective immediately postimplantation, suggesting that it may represent an abortifacient acting at an early stage of pregnancy [64]. Collaborative studies are currently being carried out with the Institute of Zoology, London to evaluate this potential effect.

It is thus obvious that more work needs to be done on plant products before the active principals can be identified, extracted and used clinically.

d) Immunologic fertility control

Research is underway to develop vaccines that will safely and effectively inhibit fertilization and effectively disrupt implantation over a period of 12–24 months. The main types of contraceptive vaccines that have been investigated are:

1. Anti-hCG vaccine

Two types of anti-hCG vaccines have been investigated [65] and studies have shown the development of antibodies to the whole B subunit of the hCG molecule. These, however, crossreact with LH, FSH and TSH. Moreover, a subsequent efficacy study showed that they were not uniformly effective in preventing pregnancy [65].

In recent years, attempts have been made to develop antibodies to specific peptide chains on the hCG B subunit, namely the hCG-specific carboxyterminal region of the B subunit of the hormone (B-hCG-CTP). Evaluation in phase I clinical trials, involving previously sterilized women, show that the levels of antibodies appears to be high enough to confer antifertility effect on fertile women [66,67]. Moreover, no serious or unacceptable side-effects were obtained. Currently, plans are being made to evaluate the antifertility action of this vaccine formulation in fertile women. The duration of the immunity elicited by the prototype vaccine used in the phase I clinical trial is several weeks to months. This is well short of the 12–24 months sought. Thus, there are plans to improve the current vaccine, notably by incorporating it into biocompatible and biodegradable slow-release delivery systems to extend its duration of action.

2. Antitrophoblast vaccine

Research is underway to develop a vaccine directed against the trophoblast of the peri-implantation embryo. Earlier studies carried out in this area isolated trophoblast membrane protein antigens of potential interest for vaccine development [67,68]. Currently, monoclonal antibodies are being used to identify, isolate, characterize and select relevant molecules more selectively. The data generated in these studies were reviewed and discussed in Toronto in 1986 [69]. As a result, a number of antitrophoblast antibodies have been selected as reagents for the identification, isolation, characterization and selection of molecules for evaluation as components of prototype antitrophoblast vaccine.

3. Antisperm vaccine

Research into antisperm vaccines has been going on for several years with little result [70]. Recently, work has been going on to identify monoclonal antibodies to isolate and characterize sperm membrane antigens that represent appropriate candidates for development into antisperm vaccines [71].

Male fertility regulation

Active research is being pursued in the following fields:

a) Hormonal suppression of spermatogenesis

Research is being pursued in the suppression of gonadotrophins by either progestogens or LH–RH analogues [72–74]. All such methods depend crucially on a slow release of long-acting androgen as they suppress testosterone secretion. The most effective steroid combination to date is DMPA and testosterone enanthate. Azoospermia was achieved in approximately 50% in clinical trials [75].

LH–RH analogues (both agonists and antagonists) represent another lead in the suppression of spermatogenesis. However, their use must again be supplemented with long-acting androgen as they suppress testosterone secretion. Moreover, they do not produce a consistent azoospermia [75].

b) Qualitative sperm changes

FSH is said to influence the functional maturation of sperm and this might provide a lead for contraceptive development. The possibility of specifically suppressing FSH by means of a single natural hormone, inhibin, remains challenging [74,76].

Again, interfering with the penetrating ability and/or motility of sperm without blocking spermatogenesis is under exploration in WHO programs but it is estimated that a long time will lapse before a suitable compound reaches clinical development [77].

c) Male pill

Clinical trials carried out in China showed the antifertility action of gossypol and indicates the possibility of a male pill [78,79]. However, the trials in China also showed a high degree of irreversibility, hypokalemia and episodes of neuromuscular disorders. Thus the present stand is to suspend studies with gossypol until analogues not having the reported side-effects are available.

Conclusion

It can be seen that it is extremely difficult to predict with certainty the future direction of contraceptive technology. Workers and 'Seers' in the field of contraceptive research predict no completely novel breakthrough in this century at least. Barring some sudden scientific breakthrough, it looks as though we have to be satisfied with the current methods for some time yet. However, what is important is that the vast amount of research going on is making a wide array of fertility regulating methods available for use in family planning programs. In this way, the needs of a wide spectrum of couples desiring contraception can be met. In fact, with additional research on the biosocial determinants of fertility, one can confidently say that the use of contraception will increase in the future.

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Resumé

On s'attend à un accroissement de la demande pour la régulation de la fécondité au cours des deux ou trois prochaines décennies car le nombre de couples qui se trouvent dans les groupes en âge de reproduire devrait augmenter d'environ un milliard dans les seuls pays en développement. L'objectif crucial pour l'avenir sera par conséquent d'optimaliser l'usage des méthodes actuellement accessibles, de les rendre sûres, efficaces et acceptables en leur apportant des modifications mineures dans la composition ou le mode d'administration. De plus, il faudra que de nouveaux progrès soient faits dans le domaine technique de la contraception.

Cet article présente une mise à jour des travaux en cours pour améliorer les méthodes actuelles de la régulation de la fécondité et les recherches entreprises sur d'éventuelles nouvelles méthodes contraceptives.

Il est extrêmement difficile de prévoir avec certitude l'orientation que prendra dans l'avenir la technologie contraceptive. Les travailleurs et les chercheurs dans ce domaine ne prévoient pas de découverte totalement innovatrice, avant la fin de ce siècle tout au moins. On espère toutefois en quelque découverte originale dans la technologie contraceptive, grâce au travail réalisé actuellement par des chercheurs indépendants. Le 21ème siècle en verra peut-être les fruits.

Resumen

Se estima que aumentará la demanda de regulación de la fecundidad durante el curso de las próximas dos o tres décadas ya que el número de parejas en edad reproductora habrá de incrementarse a casi mil millones. El objetivo crucial del futuro será en consecuencia optimizar el empleo de métodos actualmente disponibles, y hacerlos seguros, eficaces y aceptables mediante modificaciones de tipo menor en la composición o el modo de administración. Además, habrá nuevos adelantos en la tecnologiá de la anticoncepción.

En esta monografía se presentará una actualización de los trabajos en vías de realización para mejorar los métodos actuales de regulación de la fecundidad y las investigaciones que se efectúan sobre posibles métodos anticonceptivos neuvos.

Es muy difícil pronosticar con certeza la orientación que tendrá en el futuro la tecnología de la anticoncepción. Los trabajadores e investigadores de este campo no pronostican descubrimientos totalmente innovadores en este siglo por lo menos. Sin embargo, se espera algún descubrimiento original en la tecnología anticonceptiva gracias a los trabajos realizados actualmente por investigadores independientes. El siglo XXI podría quizá ver sus frutos.