Overview of advances in contraception

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For most of man’s existence, natural checks on fertility ensured that the numbers of the population more or less matched the resources available. It is only in the last few generations that man has so dominated the natural environment that the numbers of people in the world have increased exponentially, unchecked by natural disasters such as disease and starvation. Coincidental with extended life expectancy, the fertility rate of individual women has increased with the advent of bottle feeding and the decline in the contraceptive effects of breast feeding. Contraception has become increasingly important to individuals, allowing them to break free from the ‘burden of excessive fertility’.

In addition to the deleterious effect that excessive fertility may have on individuals, the impact globally is potentially disastrous. In 1999, the total world population reached 6 billion and, although the rate of growth is slowing, the most optimistic projects suggest that the total population will double to 10–12 billion before it stabilises around the year 2050. The use of contraception is increasing world-wide and by 2000 approximately 60% of couples are using contraception. However, it has been calculated that over 300 million couples world-wide do not have access to effective contraception.

A high level of contraceptive prevalence is a necessary component of the demographic changes which accompany the transition from non-industrialised to industrialised country status. Although there has been a striking increase in the range of contraceptives available in the last 50 years, the present methods are still far from perfect. Moreover, there is good evidence that when individuals can choose from a range of contraceptive methods, long-term compliance is improved. Even today, in countries such as the UK where contraception is widely available free of charge, over 50% of pregnancies are unplanned and 1 in 6 is terminated by abortion.

The prevalence of contraceptive usage is related to a range of factors including religion, political will, and economic status, as well as acceptability and effectiveness of methods. In general, the more affluent developed countries of Western Europe and North America have a high
rate of contraceptive prevalence and a low total fertility rate. As non-industrialised countries become more affluent, there is a bigger incentive for individuals to limit their family size. As a result, there are large differences in age distribution of population between industrialised and non-industrialised countries. In most Western European countries with low fertility rates and extended life expectancy, there are relatively few children compared to older people. In contrast, countries like India have a typical pyramidal population profile. These demographic changes have profound influences on the economy and society. All these factors emphasise the central role that contraception has in shaping the pattern of society and, in particular, the lives of individuals. In this chapter, I shall indicate the strengths and weaknesses of existing methods and indicate approaches which are likely to lead to new methods.

Past and future trends

Although methods of contraception have been used in societies throughout history, it is only in the latter half of the 20th century that highly effective methods which were relatively easy to use become available. The discovery of the oral contraceptive pill by Pincus and Chang in the 1950s was truly a break-through in contraceptive technology, providing a method which was highly effective, easy to use and not directly related to intercourse. For the first time, women had access to a method which was totally under their control and allowed them to enjoy sexual activity without the fear of unwanted pregnancy. The generation of women who started using oral contraceptives in the early 1960s have now completed their reproductive life and become menopausal. It is hard to appreciate now that the launching of 'the pill' provoked severe criticism from many religious groups who felt that, without the fear of pregnancy, many women would become sexually promiscuous and morally degenerate.

The pill is not only popular because it is effective, but because it is associated with many other health benefits, e.g. the reduction in menstrual blood loss, the relief of dysmenorrhea and predictability of periods. However, some women suffer minor side-effects, such as weight gain and acne, which may be sufficiently troublesome to make them seek alternative methods. Moreover, there are a number of rare but more serious side-effects, such as venous thrombo-embolism and myocardial infarction, which make it unsuitable for those at high risk.

The number of contraceptive methods which are directed at men are limited to the condom and vasectomy both of which have their limitations. Thus, although the number of methods of contraception have increased in the last 50 years, there is still room for new developments. Factors influencing the development of new approaches include social
structure such as the age of first pregnancy as well as side-effects. Ideally, new methods should not only be highly effective and totally safe, but also endow health benefits, such as protection against common diseases like ischaemic heart disease and cancer. While this may be difficult to achieve, a wide range of contraceptive methods should allow more selective prescribing, so that a safe method for the individual man or woman can be chosen. The wider the range of method, the less likely that unwanted pregnancy will occur because of non-compliance.

**Refinement of existing methods**

In the next 10 years, it is unlikely that any totally new method will reach the marketplace. The stringent requirements of efficacy and safety dictate that the time-scale for the development of a totally new drug or device from invention to marketing is long. Thus, apart from variations in the type of material in condoms, e.g. plastic versus latex, it is unlikely that a totally new method of male contraceptive will be available. The spread of sexually transmitted diseases and especially HIV world-wide has reached epidemic proportions in some countries, e.g. South Africa. There is intensive research into virucides and microbicides which, if used in conjunction with condoms, can help to reduce the risk of infection. Phase II trials of saccharide polymers, e.g. dextrin sulphate (D$_2$S), and detergent-based virucides, e.g. BCT-100 and novosome cream (Novovax), are presently on-going, but none of these compounds has potent spermicidal properties.

The pill has become a widely accepted contraceptive method which is commonly used in most industrialised countries. In the last 15 years, the dose of oestrogen has been reduced to the minimum required to suppress follicular development (equivalent of 20 μg ethinyl oestradiol). New ‘third generation’ gestogens, such as desogestrel and gestodene, have been introduced in order to reduce the incidence of side-effects associated with the androgenic effect of 19-nor derived gestogens. The modification of the gestogen to produce a more ‘oestrogenic’ pharmacological profile has led to a slight increase in the risk of deep venous thrombosis and pulmonary embolus, although the overall risk of death from such a complication remains very low when compared to pregnancy. The dose of oestrogen in the pill is now so low that follicular development recommences during the pill-free week. New developments which minimise the risk of ovulation, include reducing the pill-free interval to 4 days or extending the time of administration to 3 months – the so-called tricyclic pills. A reduction in the amount of menstrual bleeding is a very valuable side benefit of oral contraceptives. It is likely that any method which abolished or reduced the number of
periods would prove popular, at least with a percentage of the population. A recent survey asked women in The Netherlands what would be their preferred menstrual interval associated with a new method of contraception. The percentage of women who opted for complete amenorrhoea rose from 20% in 20-year-olds, to over 50% in those over 40 years. However, comparable surveys conducted by the World Health Organization (WHO) over 20 years ago in over 11 countries, mainly in South East Asia, indicated that amenorrhoea would be unacceptable amongst users and providers mainly because of the difficulty of excluding pregnancy. It would be of interest to determine whether these reservations still exist and whether the provision of a cheap, simple and reliable pregnancy test would make the method more acceptable.

Further refinements of hormonal contraception which have taken place in the last 10 years and which will be developed further are new delivery systems. Delivery of the steroids by non-oral routes, e.g. percutaneously or vaginally, bypass the first pass through the liver and, hence, have impact on metabolism. Moreover, because the drugs can be delivered continuously without the peaks and troughs characteristic of a once daily ingestion, the dose of steroid can be reduced considerably as compared to that required using the oral route. Ingenious means of delivering steroids via percutaneous patches and creams, vaginally via pessaries and rings, by subcutaneous implants and even locally via the uterine cavity, have already reached clinical practice. Silastic rings impregnated with steroids release oestrogen and progestogen at a near constant rate and provide many of the advantages of the combined pill, i.e. their use is totally under the control of the user. Menses can be delayed until socially least inconvenient, merely by deferring removing the ring which, after washing, can be re-used.

Oestrogen-free hormonal contraception can be achieved by release of gestogens from vaginal rings, subdermal implants or intra-uterine devices. The problem of unpredictable breakthrough bleeding, which is associated with all forms of gestogen-only contraceptives, has not yet been solved although trials are underway with cyclical administration of anti-progestogens.

These alternative methods of steroid delivery have adhered to the principle that it is necessary to retain regular menstrual bleeding. The major disadvantage of methods such as gestogen-only contraception involving either daily pills, injections or subcutaneous implants, e.g. Norplant® or Implanon®, is the upset in the pattern of menstrual bleeding. The unpredictable nature of the bleeding, which can vary from regular menses to irregular spotting or amenorrhoea, results in a relatively high rate of discontinuation – about 30% in 1 year. There are probably cultural differences as to whether women want or dislike menstrual periods. The morbidity associated with menstruation is impressive, e.g. dysmenorrhoea, anaemia, premenstrual symptoms and in many Western
societies menstrual disorders are the commonest reason that a women under 50 years of age consults her general practitioner. There are many health benefits associated with amenorrhoea and further research is needed into factors determining its acceptability.

A very attractive approach involves local delivery of substances directly into the uterine cavity. Gestogen loaded intra-uterine device (Mirena®) releases approximately 20 μg levonorgestrel per day - a dose insufficient to affect pituitary-ovarian function, but induces atrophy of the endometrium\textsuperscript{18}. Although there is a striking reduction in the amount of menstrual bleeding and the majority of women eventually become amenorrhoeic, unfortunately there is a significant number who suffer unpredictable ‘menstrual chaos’ especially in the first few months. Mirena® is probably the prototype of a range of impregnated IUDs releasing hormones and other drugs, \textit{e.g.} prostaglandin synthetase inhibitor, locally to the uterus.

**New methods**

**Male hormonal contraception**

Traditionally, most contraceptive methods have been targeted at women. Women have more to lose as a result of contraceptive failure being left literally ‘holding the baby’. In most species, control over reproduction is exerted through the female who go through prolonged periods of natural infertility, \textit{e.g.} seasonal and lactational anoestrus. As a result, it would appear that the female reproductive axis is more susceptible to disruption and, hence, inhibition of ovulation relatively easy to achieve pharmacologically.

In contrast, in men, spermatogenesis occurs continuously throughout life after onset of puberty and it has been difficult to develop a safe, effective method of inducing infertility. In spite of the limited range of existing methods, nearly 50% of existing couples use either the condom or vasectomy. A survey of attitudes of nearly 2000 men and women to the use of a ‘male pill’ was conducted recently in Edinburgh, Cape Town, Shanghai and Hong Kong\textsuperscript{19,20}. In all centres, both men and women welcomed the idea of hormonal contraception for men and the majority of them said that at some time they would use it.

As stated above it will be at least 5 years before a total new method of contraception is marketed. Perhaps among the first may be a ‘male pill’. The concept of using steroids to suppress spermatogenesis is not new. Over 50 years ago, Heller and colleagues demonstrated that reversible azosperma could be induced in men by injection of large doses of testosterone propionate (25 mg/day)\textsuperscript{21}. In 1990, the first large trial by
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WHO confirmed the contraceptive efficacy of this approach at least in the 60% of men who became azo or severely oligospermic\textsuperscript{22}. This approach, however, has several limitations. The supraphysiological dose of androgen required produced side-effects such as weight gain, hypertension, change in prostate size and in plasma lipids in a minority of men such that it could not be marketed for wide-spread use. Secondly, the testosterone preparation, involving intramuscular injection every 1–2 weeks, is very inconvenient. Fortunately, recent developments in formulation have provided androgen preparations, e.g. testosterone undecanoate, which would permit injection every 3 months\textsuperscript{23}.

Current research has concentrated on lower replacement doses of testosterone (4–8 mg/day) to maintain sexual function in combination with substances which suppress gonadotrophins, e.g. gestogens, antagonists of gonadotrophin-releasing hormone (GnRH)\textsuperscript{24}. Recent studies involving cyproterone acetate (2–20 mg/day) or desogestrel (300 \(\mu\)g/day) by mouth or medroxyprogesterone acetate (Depo Provera, 300 mg/3 months) have shown encouraging results, but it will be at least 5 years before the relevant phase III trials have been completed. It will be important to monitor the effect of these combinations on general health parameters, although it will probably be several years before we can determine the long-term effects, e.g. on the incidence of prostate disease.

Novel androgens are being explored which may be safer than testosterone. 7\(\alpha\)-Methyl nortestosterone (MENT) is a synthetic androgen which is more potent than testosterone on its effect on libido, muscle, etc\textsuperscript{25,26}. However, unlike testosterone, it is not metabolised to a 5\(\alpha\) reduced product (dihydrotestosterone) in some target organs and, hence, has relatively little effect on the prostate. A range of ‘androgen receptor modulators’ which bind to the androgen receptor but produce tissue specific effects, are under development and may form the basis of an androgen with ‘health promoting’ properties.

Female hormonal contraception

The use of an equivalent class of compounds – selective oestrogen (SERMS) and progestogen receptor modulators (PRM) – is the most promising approach for the development of a new method of contraception for women. Progesterone is essential for ovulation, implantation and the maintenance of pregnancy. In 1980, chemists at Roussel UCLAF announced the synthesis of RU 486 (mifepristone) a steroid derivative which antagonised the effect of progesterone\textsuperscript{27}. As early as 1982, it was shown that mifepristone would induce abortion in early pregnancy and, subsequently, it has been licensed for this purpose (in combination with a prostaglandin) in most countries in Europe, in China and most recently in
USA\textsuperscript{28}. However, the political controversy surrounding the use of the ‘abortion pill’ has hampered the development of these compounds for other purposes, including contraception. Over 200 antigestogens have been synthesised, but only mifepristone has been marketed and even then its use restricted to induction of abortion under carefully regulated conditions. All antigestogens bind to the progesterone receptor, but each differs slightly in pharmacological effect\textsuperscript{29,30}. Most antiprogestogens have agonist as well as antagonist actions and, hence, are more accurately termed progesterone receptor modulators (PRMs). Mifepristone is no exception and can induce gestogenic activity on the endometrium in the absence of progesterone (e.g. postmenopausally). However, in most situations, mifepristone antagonises the action of progesterone. In different doses, mifepristone has been shown to inhibit ovulation and transformation of proliferative to secretory endometrium, and induce menstrual bleeding in the luteal phase of the cycle and in early pregnancy\textsuperscript{31}. These properties suggest that antiprogestogens could form the basis of novel methods of oestrogen-free contraceptives. Daily administration of 2 or 5 mg mifepristone suppresses ovulation without stopping follicular development\textsuperscript{32}. In spite of normal levels of oestradiol, the endometrium becomes slightly atrophic and the majority of women are amenorrhoeic. Administration of a single dose of mifepristone at midcycle has been shown to be effective as a postcoital agent (10–600 mg) or a ‘once a month’ pill (200 mg)\textsuperscript{33–35}. Given together with a prostaglandin at the time of expected menses, it will disrupt implantation and prevent the establishment of pregnancy in the majority of women.

Although these studies have all demonstrated ‘proof of concept’, whether they are translated into a new method of contraception will be dictated by political and economic considerations. Daily low dose antigestogen potentially provides a new method of contraception which does not contain an oestrogen which is the cause of most of the serious side-effects associated with the combined oral contraceptive (COC). The reduction or absence of menses would be a health benefit and could be seen by some women as a major advantage. The use of a single dose as a postcoital agent or regular ‘once a month’ pill would provide a useful alternative for these women who do not require contraception every month or who may have contraindications to current pills.

**Long term prospects (>10 years)**

In the long-term, new approaches are likely to focus on those processes which are specific for the reproductive system (Fig. 1). In this way, pregnancy can be prevented without having effects elsewhere in the body.
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Meiosis arrest

Meiosis – the process by which the number of chromosomes in the germ cells is reduced from 46 to 23 – occurs only in the testis or ovary. There

Fig. 1 Potential targets for contraception in men and women Reproduced with permission from Baird and Glasier15.
are a number of genes which are expressed at specific important steps in meiosis, the products of which (e.g. activin) are involved with key maturational events of the sperm or egg. As the molecular basis for spermatogenesis and oogenesis is explored, it should be possible to design compounds which interfere with processes specifically in the gonad.

In the female, meiosis is almost completed before birth, but the final stages of maturation of the oocyte occurs just before ovulation. Prior to that, the oocyte is incapable of being fertilised by sperm and no pregnancy would occur. Although we know that at least one protein (c-mos) is involved in the arrest of the oocyte, we do not fully understand the molecular mechanism. The granulosa cells inhibit meiosis in the oocyte by producing high amounts of cyclic AMP (cAMP) and the levels fall during the final maturation. If this fall is prevented in rats by the administration of a compound which inhibits phosphodiesterase 3, pregnancy is prevented because the oocytes fail to acquire developmental competence. These results support the concept that it should be possible to prevent pregnancy by interfering with the oogenesis. As many of the same genes are involved in spermatogenesis, it should be possible to apply knowledge of the mechanism of oocyte maturation inhibitor to develop a similar approach in men.

**Immunisation**

The process of fertilisation involves attachment of the sperm to the egg and subsequent fusion of the gametes. Sperm attaches to proteins on the surface of the zona pellucida (such as ZP3) after exposing specific proteins of the acrosome of the spermatozoa following capacitation. Immunisation against ZP3 in marmoset monkeys will prevent pregnancy by inhibiting fertilisation. Unfortunately, a proportion of the animals develop premature ovarian failure due to loss of primordial follicles associated with an autoimmune oophritis. Immunisation agents of sperm antigens may avoid these complications, although most genes are expressed at some time in both sexes. The unforeseen consequences of provoking autoimmune reaction and the variability in response are hazards which make it unlikely that there will be much commercial enthusiasm for the development of a contraceptive vaccine for women.

Immunisation of men against proteins involved in the final maturation of the spermatozoa, e.g. fertilin, is another appealing theoretical approach. The process of spermatogenesis could remain intact, but the final mature sperm would be incompetent to fertilise an egg. Infertility due to the development of antibodies to sperm occurs spontaneously in a number of infertile men and in a proportion of men following vasectomy. The fact
that these men are otherwise perfectly well is reassuring that this approach would be safe as well as feasible. However, there is concern about whether such immunisation would be fully reversible.

Similar concerns have been raised in relation to immunisation against pregnancy proteins. It has been known for over 20 years that monkeys immunised against human chorionic gonadotrophin (hCG) or the C-terminus of the β subunit fail to become pregnant. However, the response to immunisation is variable and as the titre declines, recurrent abortions occur. Clinical studies by Talawar and colleagues in India and by the WHO have demonstrated that it is possible to immunise women with hCG linked to the tetanus toxoid, but contraceptive efficacy has not yet been demonstrated.

In summary, although there is no shortage of potential targets for immunisation to prevent pregnancy, the many risks associated with provoking autoimmunity and/or the political concern about potential misuse of vaccines, makes it unlikely that an effective contraceptive vaccine will emerge in the foreseeable future.

**Hormone antagonists**

As the molecular structure of the hormones and their receptors associated with reproductive processes is unravelled, it is likely that synthetic antagonists can be developed as has already occurred for steroids. Mutations of the follicle stimulating hormone (FSH) receptor have been described in women who present with primary amenorrhoea due to lack of follicular development. FSH is important for the initiation of spermatogenesis, although whether it is required for the maintenance in adult men is not yet clear. Inhibitors of FSH synthesis, e.g. inhibin analogues or activin, could have great potential for contraceptive use in both sexes. FSH receptors are only present in the ovary and the testis so that specificity of action would be assured. There are a number of proteins involved in the final stages of oogenesis and spermatogenesis which remain to be discovered and which could be targets for contraceptive antagonists.

**Implantation**

Implantation of the embryo in the uterus depends on a complex series of interactions between the trophoectoderm of the embryo and the decidua of the uterus. Progesterone induces the transcription of a range of genes in the uterus involved in implantation, e.g. leukaemia inhibitory factor (LIF), calcitonin, α4β, and αβ integrins, etc. In transgenic mice...
in which the LIF gene has been mutated, the embryos fail to implant due to uterine hostility. LIF is probably only one of many genes which are important for establishing successful implantation and analogues designed to disrupt their function could be contraceptive.

A very promising target for contraception is angiogenesis. The growth of new blood vessels occurs rarely in the adult animal except in the reproductive system, e.g. follicular growth and ovulation, formation of the corpus luteum and secretory endometrium. Antagonists of vascular endothelial growth factor (VEGF) prevent pregnancy in mice without producing major systemic side-effects presumably because angiogenesis only occurs specifically in the ovary and uterus at critical stages of the cycle. As antagonists of angiogenesis are very effective at slowing the rate of growth of tumours, it is likely that major resources will be invested in the development of these compounds as anticancer agents. This approach may lead to a completely new class of contraceptives.

However, there may be political and ethical constraints to the use of agents which can potentially disrupt implantation. As mentioned above, the application of antigestogens for contraceptive purposes has been hampered by protests and threats of economic boycott by groups opposed to abortion. Not every women or society would find a method which disrupted implantation (‘menstrual induction’) ethically acceptable. However, the intra-uterine device which prevents implantation is sold widely throughout the world and recent surveys of attitudes of women in industrialised and non-industrialised countries suggested that the majority would use a ‘once a month’ pill based on this principle.

Conclusions

The latter half of the 20th century witnessed a striking increase in the use of contraceptives throughout the world. Access to effective contraception is now accepted as a necessary component of reproductive health allowing individual men and women to have their desired number of children. The development and wide-spread use of hormonal contraception has played an important role in facilitating the change although there are still countries where economic, political or religious factors combine to impair easy access to effective contraception. The development of new methods is slow and expensive compared to other drugs because of the stringent requirements for safety and efficacy. It is unlikely that there will be a totally new method of contraception available within the next 5 years, but within 10 years we will probably see the first ‘male pill’. By increasing the range of contraceptive options, it is likely that individuals will find a method which suits their circumstances and, hence, avoid unplanned pregnancy.
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