historical perspective

Contraception – past and future

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Modern contraceptive methods have a surprisingly short history and are dominated by the oral contraceptive pill, which came on to the market in 1960. New developments since the advent of the pill have been largely limited to tinkering with the contents and routes of administration of hormonal contraception. The knowledge that would allow a more exciting approach to new contraceptives does exist but the will to proceed is hampered by financial, political and moral factors, and perhaps ironically by the AIDS epidemic.

Throughout history, mankind has tried to limit family size. Until the last century, this was largely achieved by behavioural modifications, including abstinence, infrequent coitus, the avoidance of intercourse during the fertile period of the cycle and coitus interruptus (the withdrawal method). In population terms, breast-feeding, which inhibits normal ovarian activity, has been one of the most important means of limiting fertility, whereas for individual couples, coitus interruptus – first mentioned in the book of Genesis – has had a major role to play. One artificial method of contraception, the condom, has a surprisingly long history. Penile sheaths were described in Egypt in 1350 BC. Originally made from animal intestines, and later from linen or silk, they were used mainly for protection from venereal disease. Not surprisingly, given the place of women in society, female barrier methods arrived much later on the contraceptive scene. The first 'womb veil' is attributed to an American working in the early 1800s and the first cervical cap was produced in Germany around 1830. It took more than 150 years before the female condom[1] came on to the market in 1993.

The intrauterine device

Until the second half of the 20th century, the only other artificial method of contraception was the intrauterine device (IUD). It was first developed in 1909 in

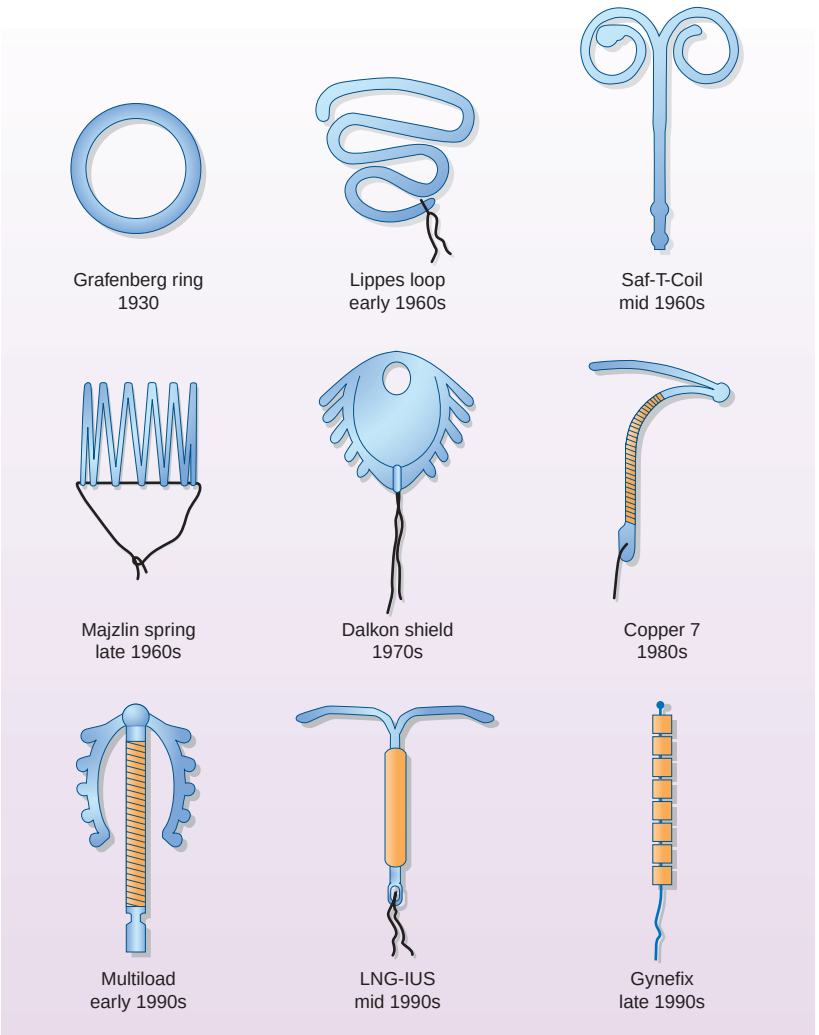

Figure 1 **Intrauterine devices through the 20th century.** Dates represent roughly the time of first availability in the UK or USA.

Germany from loops of silk-worm gut, later from silver–copper alloys and eventually from plastic (Fig. 1). The modern IUD appeared in 1969 when copper was added to the plastic frame, improving contraceptive efficacy and allowing the size of the device to be reduced[2]. Most recently, the plastic frame was removed in the belief that side-effects will be reduced through use of an even smaller device (Fig. 1)[3]. IUDs fell into disrepute in the mid-70s when a rather fearsomely shaped device with a multifilament tail – the Dalkon Shield – was shown to be associated with pelvic infection and infertility[4]. Nevertheless the IUD is one of the most commonly used methods of contraception in the world, thanks mainly to widespread use in China. Despite being highly effective, extremely safe, long-acting (IUDs are licensed for 5–10 years of use) and very cheap, the copper IUD is not popular in the USA, nor in much of Western Europe.

Advent of the oral contraceptive pill

The advent of the oral contraceptive pill, developed by Pincus and Rock and colleagues[5] and first marketed in 1960, heralded a revolution in contraception and arguably laid the foundations for women's liberation. Perhaps the most widely researched drug in the history of therapeutics, the pill has been repeatedly shown to be safe and effective[6]. It has been, and remains, a favourite subject of media hype, and despite its safety record, the majority of women still perceive the pill as potentially dangerous[7]. It is of course statistically much safer than pregnancy.

Developments in oral contraception

Much of the very recent history of contraception centres round hormonal methods. In the first two decades after the pill was marketed, research efforts were concentrated on improving safety and reducing side effects. This was achieved by lowering the dose of oestrogen (ethinylestradiol) and experimenting with different types of progestogen. The dose of estrogen has been reduced from 150 μg to 20 μg, and a pill containing 15 μg is currently in clinical trials[8]. Nervous of compromising efficacy with such a low dose, investigators have tried reducing the duration of the pill-free interval from the traditional seven days to four or five days and substituting the placebo tablet or pill-free day with a small dose of estrogen alone[9]. Biphasic and triphasic regimens (in which the dose of hormones changes two or three times throughout the 21 days of treatment) were introduced in an attempt to improve bleeding patterns and safety by mimicking the normal physiological cycle. These regimens have never proven better than monophasic pills and are indeed more complicated and more expensive.

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Most of the efforts with new progestogens have centred around producing less androgenic compounds. Ironically, this may have resulted in a slightly increased susceptibility to venous thrombosis and a marginal reduction in safety, resulting in the pill scare of 1995 (ref. 10). Drospirenone, the most recent progestogen to reach the market, has anti-mineralocorticoid properties that are reported to reduce fluid retention[11]. Heralded by the media as the pill which "makes you lose weight", rumour has it that supplies were sold out after only one month of this pill coming on to the market in Germany.

New routes of administration

Although the pharmaceutical industry still seems pre-occupied with the dose and type of steroids, research into hormonal contraception in the last twenty years has concentrated on the development of new delivery systems. Avoiding the oral route has the theoretical benefit of bypassing the first pass of metabolism through the liver and providing constant release rates of steroids. It has the very real benefits of reducing or eliminating the need for compliance and increasing choice. Injectable progestogens (depot medroxyprogesterone acetate and norethindrone enanthate) were approved in some countries in the early 1980s. Combined injectables (containing both estrogen and progestogen and administered monthly[12]) are now widely used in Central and South America and have recently been approved in the USA. Progestogen-only contraceptive implants became widely available in the 1990s. Initially marketed as six silicon-rubber-coated rods that were implanted subdermally in the upper arm (Norplant), the number of rods was reduced to two (Norplant 2, Jadelle) and finally to one (Implanon)[13]. Implanon lasts for three years and to date no method failures have been reported. The addition of a progestogen to the intrauterine device has produced an IUD that is licensed for 5 years, but which, in contrast to the copper IUD, is associated with a significant reduction in menstrual bleeding (Fig. 1, LNG-IUS)[14]. The concept of a five-year contraceptive that dispenses with menstrual periods is extremely attractive to many women in Europe. In the UK for example, the levonorgestrel-releasing device presently accounts for 11% of the hormonal contraceptive market. At the end of this long list of new delivery systems comes the contraceptive vaginal ring[15] (worn in the vagina for 21 days and removed for 7 days) and a contraceptive trans-dermal patch[16]. Both contain ethinylestradiol in combination with a progestogen and both will become available in the USA during 2002. Lagging behind (estrogen replacement therapy for menopausal women is already available in both forms) is the development of a trans-dermal gel and trans-nasal spray delivering contraceptive

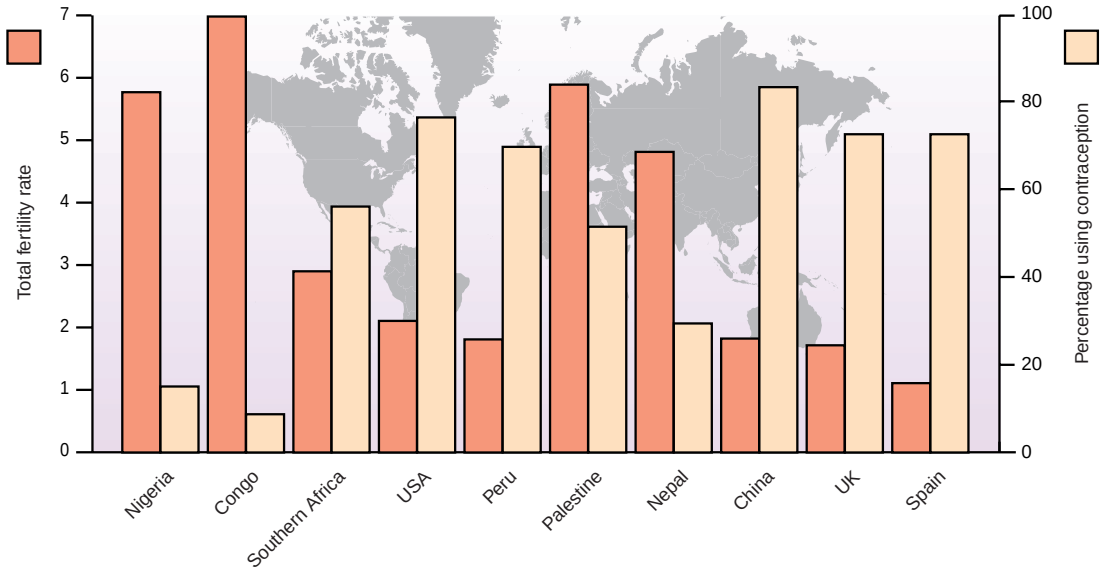

Figure 2 **Percentage of married/cohabiting women of reproductive age using contraception and average family size[28].**

hormones. If and when these become available, all the different routes of administration of hormonal contraception will finally have been exhausted and perhaps technology will move on to something that is radically different.

Health benefits of contraception

The idea that contraception can be used not only to prevent pregnancy but also to confer health benefits, and particularly to reduce the frequency of menstrual bleeding, has received considerable interest in the last couple of years. However, this hypothesis is not new. It was demonstrated in the early 1970s in Scotland[17] that women could, and would like to, run packets of oral contraceptive pills together, allowing a three-monthly, rather than a monthly, withdrawal bleed. The idea has recently been rediscovered in the USA, where in 2002, a three-monthly combined oral contraceptive pill (Seasonale, Barr Laboratories, NJ) is in clinical trials.

The potential for additional health benefits may restore the enthusiasm of pharmaceutical companies for contraceptive research. The use of selective oestrogen receptor modulators (SERMS), for example, to develop a contraceptive pill that reduces the risk of breast cancer must be very tempting.

Future prospects

Although contraceptive development seems to have almost ground to a halt with regard to steroid hormone methods for women, some exciting work has been undertaken on some different technologies. The feasibility of hormonal contraception for men has been recognised for more than fifty years[18]. It is, after all, based on the same concept as the pill. A variety of regimens have been tested, most of them (and probably the first to reach the market) comprising a progestogen to suppress spermatogenesis, combined with testosterone replacement to maintain sexual function[19]. The long delay in the development of a hormonal method for men is due partly to the lack of an appropriate long-acting form of testosterone replacement, but also to the commonly held belief that 'men would never use it' and women would never trust them to take it[20]. Although contraception is still very much seen as the responsibility of the woman, particularly in developing countries, recent surveys of men and women in Scotland, China, Hong Kong and South Africa suggest that a male pill would have a significant place in contraceptive choice[21,22]. Lured by the potentially huge market of testosterone replacement therapy for ageing men, the pharmaceutical industry has at last made some, albeit not absolutely wholehearted, commitment to the development of hormonal contraception for men.

Immunocontraception also seems to have been in the pipeline for a disproportionate length of time. Vaccination against the egg (specifically the zona pellucida), sperm and embryo (specifically β human chorionic gonadotropin) are all technically possible[23]. However, progress has been hampered by a variety of factors, including uncertainty about the long-term effects of immunizing against human tissues, and fears, perhaps ironically from women's groups, that contraceptive vaccines too easily lend themselves to coercive family planning policies.

Perhaps the greatest promise for a radically new method lies with the use of antiprogesterone. Orally active and effective as a daily[24] or once-a-month pill[25,26], the antiprogesterone mifepristone is now marketed in China as an emergency contraceptive[27]. Elsewhere in the world, its development has been seriously inhibited by the anti-abortion lobby, because the

principal use of mifepristone is as an abortion pill. The saga of mifepristone illustrates the difficulties that almost every advance in contraception has encountered. It may seem obvious, but contraception cannot be separated from sex, and everyone is interested in sex. Thus, in contrast to, say, anti-hypertensive drugs, everyone tends to have a view on contraception. Contraception is also inextricably bound up with social, cultural, moral and religious factors that often influence, if not the availability of methods, certainly their accessibility. The increasing tendency towards litigation, which even if unsuccessful, is extraordinarily expensive and time-consuming, has also served as a damper on the development and availability of new methods. All these influences make the pharmaceutical industry nervous when it comes to taking on new leads.

Impediments to contraceptive development

In recent years, research progress has depended largely on not-for-profit organizations, such as the World Health Organisation and the Population Council. However, two significant factors have had a major effect on even their enthusiasm to develop new methods. The first is the HIV/AIDS epidemic. Although it led to the renaissance of the condom and a renewed interest in the development of better barrier methods, albeit with limited scope for much improvement, it has undoubtedly reduced the interest in developing other new methods of contraception. This is partly because funds and research efforts have been sidetracked into developing microbicides, but also because of the commonly-held view that it is bordering on the 'unethical' to work on new methods of contraception that do not simultaneously prevent HIV transmission.

The second major impediment to contraceptive development has been the widespread view that the population problem has been solved, with the result that donors no longer regard contraceptive research as a priority. It is indeed true that in the thirty years between 1965 and 1995 the total fertility rate (TFR) in the world fell from 4.9 to 2.8 children per woman and that in 1997, 51 countries – accounting for over 44% of the global population – had fertility rates below the replacement level (2.1)[28]. However, the TFR in most countries of the African continent is over 5.5, and in these same countries less than 20% of married women are using contraception (Fig. 2)[28]. Despite higher contraceptive prevalence, abortion rates continue to rise in most countries worldwide, including the developed world, and unwanted and mis-timed pregnancy accounts for tens of thousands of maternal deaths each year.

As more and more women start having sex at an earlier age, delay childbearing for longer and have smaller families, many of them are destined to use contraception for more than thirty years. Most women will do almost anything to avoid an unwanted pregnancy and presently tolerate the inconvenience, side effects and albeit small risks of currently available methods. Many live in countries and have lifestyles that do not put them at risk of HIV, and in any case many would be prepared to use a method of contraception while at the same time using something else which prevents infection. Modern scientific methods can now identify genes whose products are solely involved in reproduction and which are therefore prime targets for the inhibition of conception[29]. We have the wherewithall to produce much better methods of contraception. It seems extraordinarily complacent to expect people to settle for second-best. ❑

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