

Evolutionary Voyage of Modern Birth Control Methods

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Modern birth control has been achieved with modest success via the practice of various contraceptive methods. The history of contraception can be traced back thousands of years to the description of coitus interruptus in the Bible. In modern sense, various ancient practices e.g. insertion of foreign bodies into the uterus, might seem bizarre but they did provide solid theoretical basis to the future development of contraception e.g. intrauterine contraceptive device. In this article, we illustrate how contraceptives evolve and that the old and new are really not that far apart.

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Introduction

In modern days, birth control in our community has been achieved with modest success via the practice of various contraceptive methods. According to statistics from The Family Planning Association of Hong Kong (FPAHK), the contraceptive practice rate in Hong Kong has been maintained at above 80% since 1987¹. This is higher than the world average of 60%². Family planning training emphasised on the technical aspects of education, counselling and service delivery but rarely touched on the historical development of various contraceptives. We gathered some historical memoirs through a literature search.

Withdrawal Method

Coitus interruptus, i.e. withdrawal with ejaculation afterwards, was practiced since ancient times. It was described in the Bible (Genesis 38: 7-10), that Onan was “sinful” for not following the local custom to intercourse with and impregnate his brother’s wife after death of his brother, Er. Instead, he just “went in unto his brother’s wife” but “spilt his seed onto the ground”. Coitus reservatus, i.e. withdrawal without ejaculation, was used in the ancient China and India and was thought to be beneficial to the body and soul^{3,4}.

Natural Family Planning

Back in the 19th century, people started to monitor changes in basal body temperature and cervical

mucus consistency to time ovulation. The adoption of these combined indices for natural family planning was formally defined and promoted by the World Health Organization (WHO) in the 1970s⁴.

Spermicides

In ancient Egypt and Rome, tampon soaked with various plant extracts, juices, honey, lactic acid and so on were placed in the vagina to prevent women from conceiving. These were described in the Kahun Papyrus dated back to 1850 BC, the Ebers Papyrus in 1550 BC and the Berlin Papyrus in 1300 BC. Some 3000 years ago, elephant and crocodile dung were used in India and Egypt as a suppository to be inserted in the vagina prior to intercourse. The dung probably acted as a crude barrier and its high acidity might have provided some spermicidal activity^{3,5}.

Various spermicidal pessaries were commercially available in the 19th century, and they gradually evolved into the various modern forms including foams, suppositories, creams, jelly and vaginal films⁵. Nonoxynol-9, the most commonly used spermicide nowadays, has been available since the 1950s.

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Spermicide-containing sponges were developed in the 1970s³⁻⁵.

Barrier Methods

Male Condom

Historical monuments from the ancient France and Egypt had revealed the use of penile sheaths, although the purpose was not known. These were more likely worn as a symbol of status or rank or perhaps even as protection against insects. Legendary tales ascribed the word “condom” originated from a Dr Condom, a physician who was purported to have invented the condom during the reign of King Charles II (1660-1685). He developed the cloth sheath for King Charles II who was troubled by the large number of illegitimate children he was siring. Others thought that the word came from the Latin “condus” or the Persian word “kondu” which denote a grain-storing vessel. Since the 18th century, sheaths made of cloth or animal membranes were mass-produced. Rubber condoms were introduced in the 19th century, followed by the modern latex condom in the 20th century³⁻⁵.

Female Barriers

Cervical cap — Casanova in the 18th century advocated the use of a half lemon, from which the pulp had been extracted, to be fitted over the cervix. In 1838, Frederick Wilde, a German gynaecologist, designed a rubber cap to fit over the cervix. By the end of the 19th century, cervical caps were produced in a range of sizes and shapes using a variety of substances like latex, rubber, plastic, chrome and even silver³⁻⁵.

Diaphragm — In 1882, Wilhelm Mensinga from Germany developed the diaphragm. This has since become a popular birth control method since 1920, until the 1960s when other more effective contraceptives emerged³⁻⁵. Both the cap and diaphragm were rarely used nowadays.

Female condom — The first female condom, known as “Capote Blanco” was available in the United Kingdom in the 1920s. In the 1960s, another design named “Acpote Anglaise” was marketed. However, they remained unpopular due to their relatively crude design. In the 1980s, the increasing awareness of sexually transmitted infections including HIV increased the

demand for female-initiated protection, and a refined form, currently available as the Femidom (The Female Health Company, Chicago [IL], USA) evolved^{6,7}.

Intrauterine Contraceptive Device

The predecessor of modern intrauterine contraceptive device (IUCD) was a variety of utero-vaginal devices, intracervical devices and cervical plugs used in the early 20th century. Infection and cervical erosion occurred often due to the poor construction of the devices using poor quality metals or plastic and women’s improper use of the devices. Hence they were deserted.

The concept of placing a foreign body in the uterus was first described in legendary tales about African travellers who put tiny pebbles into the uterus of camels to prevent them from getting pregnant during long desert journeys. The first IUCD was described by Dr Richard Richter in 1909, which was made of dried silkworm gut wound into a ring-shaped device. However, the use of Richter’s ring was also associated with infective risks thus it was not widely used. Later in 1926, Dr Ernst Gräfenberg produced a silver ring, subsequently called the Gräfenberg ring. Dr Gräfenberg was the first one to study ring-IUCD through scientific trials and a low failure rate of 1.6% was reported^{8,9}. Yet, his invention remained unpopular until the late 1950s when favourable long-term results were reported from large case series. Substituting with other materials, a flexible nylon ring made by Dr Zipper in Chile and a stainless steel ring invented by Herbert Hall emerged both in 1962. The Hall-ring is still the popular IUCD used in mainland China nowadays^{3-5,8,9}.

Over the years, researchers tried myriad shapes and materials for IUCDs, attempting to improve its function. The first thermoplastic IUCD, called Gynecoil, was developed in 1960 by Lazar Margulies. The second plastic IUCD, invented by Dr Jack Lippes, soon followed. The double-S-shaped silastic Lippes Loop was once extremely popular worldwide. Modifications into various shapes were made subsequently.

The history of inert IUCD would be incomplete without mentioning the Dalkon Shield (A.H. Robins Inc., Richmond [VA], USA) developed by Dr HL

Davis in 1970. Serious infections were reported from users as a result of the wicking effect of its multi-filament string that promoted bacterial ascent. The United States Food and Drug Administration banned this device in 1974^{3-5,8,9}.

A new era of IUCD design soon began, using smaller devices to reduce side-effects like dysmenorrhoea and menorrhagia. The reduced effectiveness associated with the use of a smaller device was overcome by adding metals to the plastic frame. The copper-T IUCD emerged through the combined effort of Drs Howard Tatum and Jaime Zipper. Tatum proposed the T-shaped design to fit the contour of the uterine cavity, which reduced discontinuations for pain and bleeding. However, Zipper observed a high pregnancy rate with this plastic-T device. After discovering the anti-fertility effect of intrauterine copper ions in rabbits, Zipper then added a copper winding to the stem of the plastic-T, leading to the production of the first copper-T, called TCu200, in 1969. A number of other models and variants (e.g. the copper-7, Multiload; NV Organon, The Netherlands) of copper-IUD then followed. Models of longer duration were gradually made with higher copper load, and now there are models of 10-year duration (e.g. Cu-T380A)^{3-5,8,9}.

Substituting the copper with progesterone in T-devices was studied since the late 1960s. The earliest progesterone-releasing IUDs, namely Progesteron-T (not in market now) and Progestasert (Alza Corporation, Mountain View [CA], USA), were marketed in 1970 and 1977 respectively, but their use was limited due to the short effective lifespan of 1 year. Replacing progesterone with a levonorgesterol (LNG)-releasing reservoir, the LNG-intrauterine system (Mirena; Levonorgestrel-intrauterine system, Schering AG, Berlin, Germany) with 5-year duration was produced in 1990. This marked a new era in IUCD use, as this offered additional non-contraceptive benefits such as reducing pelvic infections and treatment of menorrhagia^{3-5,8,9}.

The frameless IUCD was introduced in 1984 by Dr Dirk Wildemeersch from Belgium. This consisted of copper sleeves on a polypropylene filament whose proximal end is anchored to the fundal myometrium with a knot. This minimised side-effects such as dysmenorrhoea and menorrhagia, due to enhanced dimensional compatibility with the uterine contour^{3-5,8,9}.

In Hong Kong, the first IUCD was introduced at the FPAHK in 1963 and quickly gained wide acceptance. In those early days, inert IUCDs (e.g. the Lippes' loop,

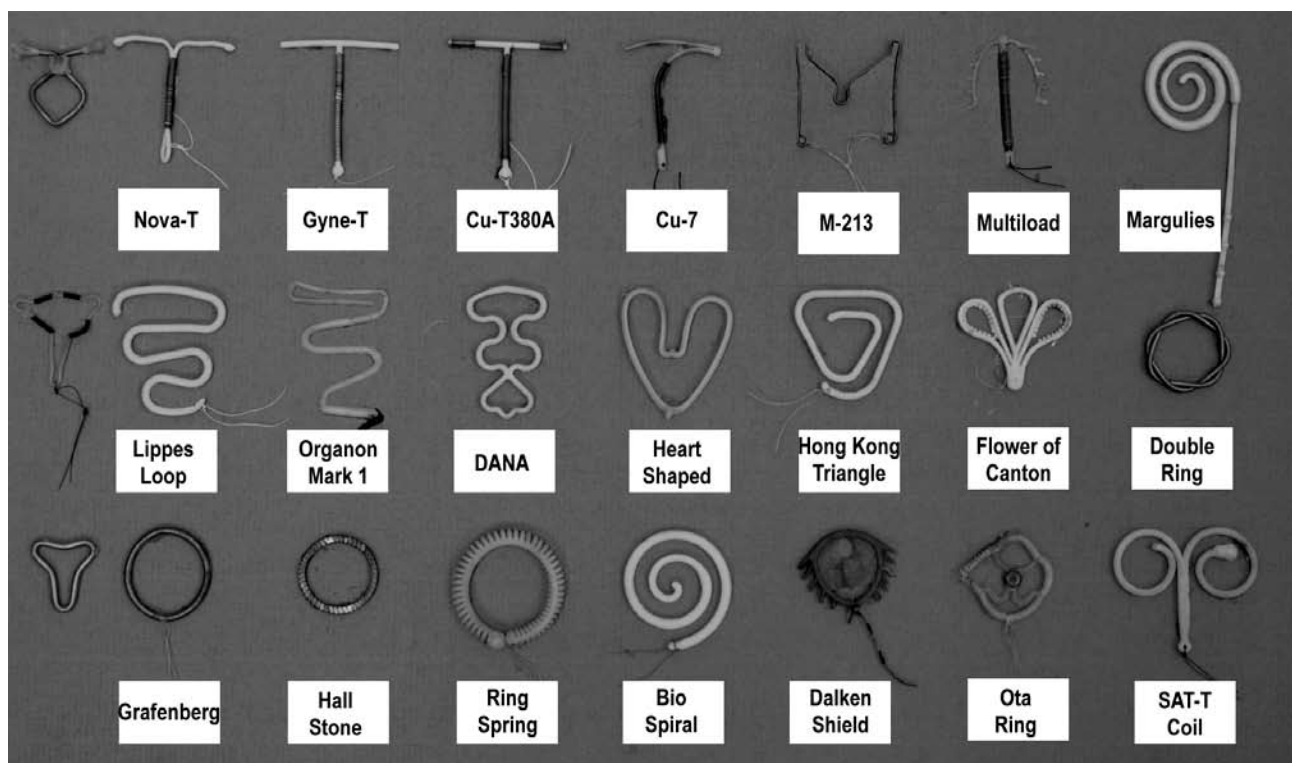


Figure 1. Archive of IUCD collection in the Family Planning Association of Hong Kong

the stainless-steel Hong Kong triangle, the M-shaped and heart-shaped coils) were the most widely used till the early 1970s. The Dalkon Shield was used in FPAHK from 1971 without significant complications apart from a slightly higher perforation and translocation rate¹⁰. It was discontinued in 1974. The copper-T IUCD came into use since the 1970s and still remained most popular now. Mirena was launched in Hong Kong in 1998. The frameless IUCD (GyneFix; Contrel, Ghent, Belgium) was introduced at the FPAHK in 2002¹¹. A collection of IUCD archived in FPAHK is shown in Figure 1.

Hormonal Contraception

Combined Oral Contraceptive Pill

The development of the modern hormonal contraceptives owed largely to the understanding in reproductive endocrinology since the turn of the 20th century. In the 1920s, Dr Ludwig Haberlandt and Dr Otfried Otto Fellner separately reported that ovarian tissue transplantation and administration of oestrogen extracts could render experimental animals infertile. Their findings were replicated by other scientists in the 1930s who recognised that both oestrogen and progesterone caused anovulation. Through the hard work of several renowned researchers in steroid chemistry, among whom were Dr Russell Marker, Prof Carl Djerassi, Dr Gregory Pincus and Dr Min-Cheuh Chang, synthetic progesterone and oestrogen were produced. By 1957, both norethindrone and norethynodrel (synthetic progesterones) were commercially made for contraceptive use, but the products were subsequently found contaminated with mestranol (an oestrogen). Coincidentally, attempts to remove the mestranol 'contaminant' yielded more breakthrough bleedings and higher failure rate, thus consolidating the concept of combined oral contraceptive (COC) pill³⁻⁵.

The first COC preparation, called Enovid (Searle & Co., Chicago [IL], USA), which contained 0.15 mg mestranol and 10 mg norethynodrel, was available in 1959 but now discontinued; the oestrogen dosage was much higher than pills used nowadays. In Hong Kong, Enovid was introduced as the first COC at the FPAHK in September 1959 on a clinical trial basis. Significant side-effects including thromboembolic risk were soon recognised in the United Kingdom and United States, leading to the development of newer pills with successively lower dosages of oestrogen which were

found to be equally effective while bringing down side-effects and maintaining good cycle control. The 0.05 mg ethinylestradiol (EE) pills were available since 1961, and the 0.03 mg EE pills were in regular use since 1972. The ultra-low-dose pill containing 0.02 mg EE was first introduced in 1974 but was initially not favoured due to poor cycle control; it was only reconsidered in the 1990s^{4,5,12}.

Like that of oestrogen, the dosage of progesterone has also been reduced while maintaining the endometrial-protective effects. However, further reductions would likely compromise ovulation suppression. The estrane progesterones were later replaced by second-generation progesterones (e.g. norgestrel, levonorgestrel). Third-generation progesterones with lower androgenic properties (e.g. gestodene, desogestrel and norgestimate) were introduced since the 1980s. The COC containing a fourth-generation progesterone, drospirenone, was recently introduced in 2002. It has anti-mineralocorticoid (hence counteracting water-retention effects of oestrogen) and anti-androgenic effects^{4,5,12}.

Other special formulations of COC have also been developed. The biphasic and triphasic COCs were introduced in the 1970s, with an aim to "mimic the natural hormonal cycle" so as to minimise the total progesterone dose while maintaining good cycle control and contraceptive efficacy. Yet, these synthetic hormones were nowhere close to natural and the clinical effect was the same as other monophasic pills. Recent interest focused on the extended-cycle formulation to reduce frequency of menstruation thus its related problems like blood loss, premenstrual tension and to give more convenience to women. A 3 monthly-cycle preparation (Seasonale; EE 0.03 mg + levonorgestrel 0.15 mg; Duramed Pharmaceuticals Inc., Pomona [NY], USA) was marketed in the USA in 2003, and similar extended-cycle formulations of other hormone combinations are on trial^{4,5,12}.

Injectables

Depo-medroxyprogesterone acetate (DMPA, Depo-Provera; Medroxyprogesterone acetate 150 mg; Pfizer, New York [NY], USA) was the first injectable hormone developed. It was marketed in 1954 for the treatment of endometriosis and threatened habitual miscarriages. Subsequently its anti-fertility effect was

observed, and it was licensed for contraceptive purpose in the mid-1960s. DMPA was introduced at FPAHK since October 1967. It soon gained popularity for its good efficacy and convenience.

After the development of DMPA, a few formulations of combined oestrogen and progestogen injectables were developed since 1963 to reduce cycle irregularity. Two such preparations, Cyclofem (also known as Lunelle in the USA; medroxyprogesterone acetate 25 mg + oestradiol cypionate 5 mg; Pharmacia Pharmaceuticals, NJ, USA) and Mesigyna (norethisterone enantate 50 mg + oestradiol valerate 5 mg; Schering AG, Berlin, Germany) had been extensively studied by the WHO but are not licensed in Hong Kong. The only combined injectable available in Hong Kong is Nonestrol (dihydroxyprogesterone acetophenide 150 mg, oestradiol-17-enanthate 10 mg; S. Venus Enterprise & Co., Hong Kong). The Chinese Injectable No. 1 was studied in mainland China since the 1980s and had remained popular in China^{5,8}.

Other Non-oral Hormonal Contraceptives

Apart from oral, injection and intrauterine routes, other modalities of hormonal contraceptive have been developed. Norplant (levonorgestrel 36 mg; Wyeth Pharmaceuticals Inc., Philadelphia [PA], USA), the first contraceptive implant, was studied since the 1960s and was approved by the WHO in 1984. It is a multi-rod subdermal implant. A single-rod implant, Implanon (etonogestrel 68 mg; NV Organon, The Netherlands), was launched in 1998. FPAHK had participated in its pre-launch trial from 1991 to 1992 but few women were recruited within 18 months. The difficulty in recruitment reflected women's preference over other contraceptives. The manufacturer had not applied for the license in Hong Kong. Both Norplant and Implanon are non-biodegradable hence need to be removed after a few years. Currently, scientists are researching for a biodegradable implant^{5,12}.

Newer hormone delivery systems, namely the transdermal patch (Ortho-Evra; norelgestromin 150 mcg + oethinyl oestradiol 20 mcg; Ortho-McNeil Pharmaceutical Inc., Raritan [NJ], USA) and the vaginal ring (NuvaRing; EE 2.7 mg + etonogestrel 11.7 mg; NV Organon, The Netherlands) have been recently marketed in the new millennium. In Hong Kong, the Evra patch

was available since 2003 and the launch of the vaginal ring is still being awaited. These offer alternative choices to suit individual preferences in the mode of use.

Anti-progestins

The use of mifepristone, an anti-progestin, as a regular oral contraceptive has been investigated. A daily low dose (2 mg) has been found effective in suppressing ovulation, so as a single monthly 200 mg dose taken in the early luteal phase. However, these are still on trial basis¹³⁻¹⁵.

Emergency Contraception

Since ancient times, special manoeuvres (e.g. sneezing, jumping) and vaginal douching with various substances (e.g. disinfectants, lemon juices or Coca-Cola) had been used for post-coital contraception. The modern hormonal method for emergency contraception (EC) probably rooted in the 1920s when postcoital administration of oestrogen in animals helped preventing pregnancy. The first reported use of EC was in the early 1960s, when high-dose diethylstilbestrol was given. It was effective but was soon abandoned because of teratogenicity¹⁶. Human studies on the use of high-dose oestrogen for EC were first reported in the 1960s. In 1972, Albert Yuzpe from Canada studied the combined regimen of 100 µg of EE and 1 mg of dl-norgestrel for EC. The Yuzpe method soon became the most popular EC regimen due to its convenience. The major side-effects were nausea and vomiting caused by the high oestrogen dose¹⁶⁻¹⁸.

The first randomised controlled trial in the world using progestogen-only regimen (LNG) was conducted in FPAHK and the results were published in 1993¹⁹. The clinical efficacy was confirmed by a multinational, multicentre trial coordinated by the WHO and the results were published in 1998²⁰. LNG-only EC is now the first-line hormonal EC²¹. It is superior to Yuzpe method because of less side-effects and higher efficacy^{19,20}. In Hong Kong, it was licensed in July 2002 and was in routine clinical use at the FPAHK since 2003¹⁶.

The use of the copper IUCD for EC had been reported since 1976. No research evidence for the use of progestogen-releasing IUD as EC is yet available¹⁶⁻¹⁸.

Studies on the use of 600 mg mifepristone within

72 hours of unprotected intercourse for EC began in 1992. The latest trial conducted by the WHO reported that lower doses, down to 10 mg, were equally efficacious²². However, its use is limited by its availability. It is only licensed in a few countries worldwide, and not yet in Hong Kong.

Conclusion

Contraception is an ever-evolving subject with new advances and improvements constantly brought into

scene by continual researches. Looking into the future, we look forward to betterment in terms of contraceptive efficacy, convenience and ease of use, acceptability and accessibility, and reduction of side-effects.

Acknowledgements

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