

Half a century of the oral contraceptive pill

Historical review and view to the future

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Throughout the history of medicine, thousands of drugs have been developed, but only one has been influential enough to earn the title of simply, *the pill*. Introduced in May 1950, the oral contraceptive pill is a medical innovation that has dramatically transformed generations. Women have gained incredible freedom and reproductive autonomy. The birth control pill separated sexual practice from conception, forcing re-assessment and reevaluation of social, political, and religious viewpoints. We take this occasion to review the humble beginnings of the birth control pill and discuss the future implications of reproductive choice in 2012 and beyond.

Historical perspective

Animal experiments in the late 1930s demonstrated that high-dose progesterone could arrest ovulation. Chemist Dr Carl Djerassi synthesized progestin from an extract of Mexican wild yam root in the late 1940s, and the concept of arresting ovulation in women became reality. The 1950s, however, was a time of very little choice for women. Even if a woman was fortunate enough to make it to university, she would often attain a career primarily as a wife, with the prospect of 3 decades of childbearing. The pill was initially marketed for “cycle control” for good reason—socially, legally, and politically, contraception was taboo. In the United States (US), the Comstock Law effectively prohibited public discussion and research about contraception. This was a controversial and outdated law, established in many US states since 1873, that defined *obscenity* and was enacted to control the sale and distribution of obscene materials. It essentially lumped talk about contraception with pornography. In Canada, under the 1892 Criminal Code, any discussion of birth control was illegal and in fact was considered obscene, “tending to corrupt morals.”¹ Although the pill was available by 1960 for “menstrual regulation,” it was not legal to discuss contraception or prescribe the pill for the indication of contraception until 1969, when the Canadian parliament decriminalized contraception by passing amendments to Section 251 of the Criminal Code.^{2,3} Physicians at the time could prescribe hormones for any reason other than birth control (eg, cycle control or menstrual irregularity). If they prescribed the pill for birth control, they were breaking

the law. In 1968, Pope Paul VI released the Catholic Church’s first official position on the birth control pill. *Humanae Vitae (Of Human Life)* condemned the pill as an “artificial” means of birth control and, thus, as sinful.⁴

One Canadian who challenged the laws by breaking them was Elizabeth Bagshaw. She graduated from what would later become Women’s College Hospital in Toronto, Ont, in 1905 as one of the first Canadian female physicians. A founding member of the Federation of Medical Women of Canada, she served as Medical Director of the first (and illegal) Canadian birth control clinic for 30 years. At the time of its opening in 1932, the possibility of a birth control pill was likely only a dream for its founders. Dr Bagshaw was inducted into the Medical Hall of Fame in 2007 in recognition of her many accomplishments over a 70-year career, including being the oldest practising physician when she retired at the age of 95.

Ironically, initial clinical investigation of the pill was driven by 2 devout Catholics in 1954. Dr John Rock, supported by women’s health advocate Margaret Sanger, performed an early trial of the pill in 50 Boston, Mass, women under the guise of a fertility study. The cumbersome US laws made this a difficult feat. Dr Rock and another early pill researcher, Dr Gregory Pincus, looked to Puerto Rico, with its perfect mix of overpopulation and no prohibitive laws. The first real large-scale trial of the pill was conducted in 1956 in Rio Piédras, a Puerto Rican housing project. The 200-plus women involved in the trial received little information about the safety of the product they were given, as there was none to give, and no one thought that it might be necessary to provide such information.⁵ That was the standard of the day. Women who stepped forward to describe side effects of nausea, dizziness, headaches, and blood clots were discounted as “unreliable historians.”⁶ Despite the substantial positive effect of the pill, its history is marked by a lack of consent, a lack of full disclosure, a lack of true informed choice, and a lack of clinically relevant research regarding risk. These are the pill’s cautionary tales.⁶

The pill brings change. The pill was first prescribed exclusively for cycle control, and only to married women. Early iterations of the pill had drastically different dosages. The first marketed pill, Enovid 10, contained 9.85 mg of the progestin norethynodrel and 150 µg of the estrogen mestranol.⁷ Today’s pills contain

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dramatically lower hormone doses—0.1 to 3.0 mg of modern progestins and 20 to 50 µg of estrogens. The progestins used today are much more pharmacologically specific and more focused in their drug effect. While current progestin doses are not directly comparable, the doses for both the original pill ingredients have fallen many-fold from those of the original recipe. Safety concerns were raised as early as 1934 regarding venous thromboembolism (VTE), and were raised again in the Puerto Rican trials, but by 1967, serious side effects were just being acknowledged. Meanwhile, the sexual revolution of the 1960s had been launched and women supposedly became as “sexually free” as men. The pill prompted fear of “sexual anarchy,” and fear that it would encourage female promiscuity.⁸ The reality, however, was that women could finally exercise control over their own bodies, plan their families, and start professional careers.

In the 1970s, the women’s movement was in full effect. Empowered women began to take charge of their own health, influenced by publications such as the *Birth Control Handbook*, a how-to guide from the students at McGill University in Montreal, Que. Published in 1968, it grew to international fame for the audacity showed by including self-determination on issues of contraception as well as feminist interpretations of the laws of the time.⁹ Another book, *Our Bodies, Ourselves*,¹⁰ grew from the grass-roots Boston Women’s Health Book Collective and became the bible of the feminist women’s health movement. Informed women demanded family planning, and protests by activist women helped to drop initial pill estrogen doses and to develop requirements for pill package labeling.

Public trust of medicine was shattered by the self-determination envisioned in the feminist movement, and Barbara Seaman’s *The Doctor’s Case Against the Pill* publicly outed the scandal of trials performed without informed consent and hushed side effects.⁶ Public trust in the medical world was shaken again in 1974 by the dangers discovered after marketing the Dalkon Shield intrauterine device.¹¹ This nonhormonal birth control method proved to have risks of permanent infertility and had to be pulled from the market after 3 short years. Safe choices in contraception remained a tricky issue. By the 1980s, however, women began to have expanded choice with the introduction of new doses, new progestins, and new multiphasic pills. Alongside these changes and within this climate of uncertainty, acceptance of family planning was the norm, and women were now substantially increasing their numbers in medicine and other professional careers. Birth control clinics were abundant and often staffed by female physicians. A notable example is Dr Marion Powell, who is often referred to as “the mother of birth control in Canada.”¹²

Development of new methods. The pill cleared the way for the introduction of an expanded range of hormone-based contraceptives. It also provided valuable data about the potential uses and side effects of estrogen-based therapies. By the 1990s, there was steady demand for the pill, and new hormone delivery systems were released—implants, intrauterine systems, injectables, and rings. Implants were on the market in Canada only from 1991 to 2000; they were removed owing to concerns about contraceptive efficacy due to manufacturing problems. They remain available worldwide and will one day return to the Canadian market. In 1992, injectable medroxyprogesterone acetate (Depo-Provera) was approved for use as a contraceptive agent. The 2000s brought contraceptive patches and rings to Canada, and research on sprays and gels elsewhere worldwide.

Concern about side effects. With these developments came concerns about bone density side effects from injectables and fear of VTE from patches. Neither of these risks were ultimately verified by actual outcomes in actual women; we discovered, sadly, that our cautious labeling laws required that package warnings be placed without adequate outcome evidence. The World Health Organization, the Society of Obstetricians and Gynaecologists of Canada, and the American Congress of Obstetricians and Gynecologists advised health care providers that concerns about bone mineral density loss should not prevent injectable medroxyprogesterone acetate use, as bone loss was typically within less than 1 standard deviation of the norm and was a reversible effect.¹³ Neither the 2006 VTE black-box label for patches, warning of presumed risks of higher transdermal blood estrogen levels, nor the concerns about novel progestins, had enough demonstrated risk to preclude using these birth control methods. Indeed, recent studies have shown the difference in risk to be negligible compared with oral contraceptives for women younger than 39 years of age.¹⁴ The huge importance of the effect of the pill had allowed for one very large in vivo experiment on women.

Risk-benefit perspective

The pill’s legacy highlights the ethical and legal consequences of postmarketing research; fear was used to emphasize non-clinically relevant outcomes.¹⁵ Initial studies reported anecdotal information about side effects; however, these were considerably downplayed. As time passed and the use of the pill increased, these risks became irrefutable. More than 50 years later, we have safer and lower-dose medications to offer, as well as an improved understanding of the risks and benefits of the pill. More important, counseling and patient education guidelines have evolved to reflect these risks.

Venous thromboembolism is one of the most notorious side effects of the pill. While it is a very real and dangerous condition, the risk should be viewed in context. The risk of VTE in a normal pregnancy is approximately 30 in 10000; with the use of oral contraceptives it is 9.1 in 10000.¹⁶ It is interesting to note that taking the pill lowers a woman's risk of VTE compared with the usual risk during a normal pregnancy. We rarely hear about this protective aspect of the pill.

Similarly, that risk needs to be considered in a broader context: the annual risk of death for a non-smoking young woman aged 15 to 34 years taking the pill is 1 in 1 667 000; the risk of a rare event like dying from a lightning strike is 1 in 2 000 000.¹⁷ This lower-risk situation describes most pill users today. We are now extremely cautious about use of the pill in women who smoke, particularly as age increases. Even if that woman is a smoker older than 35 years of age, she has a risk of death from the pill of 1 in 5200 (in comparison, the risk of dying in a car accident is 1 in 5000).¹⁷

In addition to VTE risk, evidence for other serious adverse effects of the pill has emerged—both expanding our understanding of hormonal therapies and prompting lower-dose formulations. Estrogens were found to have a dose-dependent effect on lipid profiles.¹⁸ Oral contraceptive use is also linked to cervical, breast, and liver cancers.¹⁹ In women who have ever used the pill before a first full-term pregnancy, there was an increased rate of cancer of 0.6 to 1.76 per 10000 women (95% CI 0.92 to 1.67).²⁰ While these numbers seem small, small risks matter to individuals when being counseled by their family doctors.

Small risks might also be balanced by large benefits. In addition to the overwhelming effect of contraception and reproductive rights the pill conferred to women, there are numerous non-contraceptive benefits.²¹ Oral contraceptives provide a noninvasive option for managing the vast spectrum of dysmenorrhea, menorrhagia, and perimenopausal and premenstrual symptoms. Rates for hysterectomy done for reasons of uncontrollable bleeding have substantially dropped, deaths have been averted, and lives have been made productive as a consequence of known (non-contraceptive) hormone benefits.¹⁶ Hormonal contraceptives are actually protective against ovarian and uterine cancers.²¹ The overall advantage remains substantial and is considered to far outweigh the risks for most women. It is for this reason that some groups are exploring the possibility of over-the-counter access to the pill in North America, with over-the-counter options similar to emergency contraception (ie, the “morning-after pill”).²²

The danger of unplanned or unintended pregnancy to women and their babies costs lives, not to mention

increases abortion rates, increases complications from illegal abortions, and increases crime, violence, family dysfunction, overpopulation, poverty, and ecological burden.²³ Putting total risk into perspective requires considering that family planning is not a luxury and is not a benefit only to women, but to society as a whole.

Future directions

Much appears to have changed in half a century, but not a lot really has. The doses and delivery methods of contraception have changed, but the paradigm has not. Being responsible for the burden of both the expense and the health risk of contraception has had a high cost for women. We look forward to a more equal and equitable distribution of risk and responsibility in the future.

One of the important advances in recent contraception strategies has been the development of long-acting reversible contraception. This category includes copper intrauterine devices, progestogen-releasing intrauterine systems, injectables, and implantables. They free women from having to keep track of contraception on a daily or routine basis owing to their long-term and “forgettable” nature. They are also considered to be cost-effective compared with shorter-term modalities such as the pill and condoms. They are also safer than more permanent methods such as tubal ligation, which requires intra-abdominal surgery. However, as with all contraception methods, satisfaction rates are improved with appropriate counseling.²⁴ More work is still to come on male hormonal contraception, including long-acting reversible methods.

Despite these advances, it still means that women alone are planning and executing the contraception method in more than two-thirds of cases. Including shared methods and male condom use, which women often negotiate, women are involved in more than 90% of all contraceptive use.²⁵ While not having this burden might be a boon to men, at the same time, men lose autonomy by not being responsible for contraception. Indeed, in a new era of paternity testing and legal complications of child support, some men have expressed a need to protect their own interests by asserting their own roles in contraception. To our knowledge, the demand for male contraception has not been formally studied, although several websites have been launched to capture and quantify this demographic (eg, **MaleContraceptives.org** is a project of the Male Contraception Coalition, whose mission is to help speed the development of new contraceptives for men). An effective contraceptive method for men would be one way for men to share the responsibility. Recently, there has been more media attention directed toward innovation of male contraceptive options. However, there are many international studies of male hormonal contraception and devices from as early as the 1970s.²⁶

One method that appears close to commercial reality combines an annual implant of progestin and shots of androgen every 3 months. Nonhormonal methods have also shown promise. Since 2005, there have been 2 in-office procedures available that block sperm passage—reversible inhibition of sperm under guidance, which uses an injected gel, and the intra vas device, which involves small intraluminal plugs. Still, we are far from where we could be. Most recently, Dr Tsuruta’s team at the University of North Carolina in Chapel Hill reported animal studies that demonstrated the use of ultrasound to temporarily destroy sperm, a technique that evolved from a discovery made in the 1970s.²⁷

Women’s bodies have forever been manipulated to control fertility—whether effective or not, or safe or not. As we celebrate the more than half a century of the pill, we can reflect on its legacy and its importance for patients, their families, and the planet, which logged its 7 billionth inhabitant in the fall of 2011. We can recall the cautionary tales it told from its origins to its current variations. The pill led the way but we need creative exploration of choice, access, and safety in controlling fertility for the future.

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Competing interests

Dr Liao is a former and **Dr Dollin** is an active board member of the Federation of Medical Women of Canada.

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