Fifty Years of ‘‘the Pill’’: Risk Reduction and Discovery of Benefits Beyond Contraception, Reflections, and Forecast

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Widely regarded as a revolutionary drug in its early years, “the pill” may be considered the first designer or lifestyle drug. Approximately 85% of women in the United States will use an oral contraceptive (OC) for an average of 5 years. Since the introduction of OCs in the 1960s, both health benefits and safety concerns have been attributed to their use. Widespread use of OC formulations by women throughout their reproductive life cycle gave rise to concerns about the effects of OCs on risk factors for cardiovascular disorders and cancer. In most instances, the noncontraceptive benefits of OCs outweigh the potential risks. As with many first in class drugs, lessons can be learned from its development and use. Indeed, “the pill” played a significant role in reshaping the regulatory process for new drugs during the second half of the 20th century. The birth control pill celebrates its 50th birthday this year, as women and men celebrate five decades of this revolutionary method of family planning. Recent scientific and technological advances in genomics, proteomics, new materials, and new drug delivery systems, along with a new understanding of reproductive biology, offer the promise of new, safe, and effective forms of contraception. In addition to the history of OC therapeutic advances and unintended side effects, the noncontraceptive health benefits that women experience beyond pregnancy prevention are discussed. This article summarizes a symposium presented at the 50th Anniversary of the Society of Toxicology National Meeting, held from 6 to 10 March 2011 in Washington, DC.

Key Words: risk reduction; oral contraceptive; safety.

BACKGROUND AND PERSPECTIVE

Almost half of all pregnancies in the United States are unintended or unplanned (Abma et al., 1995; Henshaw, 1998). However, from the time of the first clinical trials to the present, nearly 200 million women have taken various formulations of the contraceptive pill, making it one of the most widely consumed classes of drugs in the world. By the end of the 20th century, oral contraceptives (OCs) had become a feature of everyday life, with women reaching for their pill packet on a daily basis around the globe. It has been argued that the invention of an easily accessible method of contraception resulted in a social revolution. Now, after 50 years of availability, we revisit the implications of women who were not sick self-administering a drug, how the drugs have been modified based on safety concerns, and the emergence of health benefits separate from those related to reproduction.

No product is so universally recognized as “the pill.” Making its appearance as the first Food and Drug Administration (FDA) approved OC pill in 1961, Enovid revolutionized society. The first pill was a culmination of many years of research, ironically to aid infertility, and was surrounded by social and religious controversy. From a medical perspective, there were great debates over the risks and benefits to healthy women taking such a drug over long periods of time. Over the last 50 years, OCs have been refined, reducing the number of side effects, and the benefits beyond pregnancy prevention have become more apparent. Since its inception, chemical contraception has gone beyond “the pill” to include implantable devices, vaginal rings, injectable medications, and a transdermal patch. Initial concerns about potential for the development of cancers and thromboembolism resulted in the modification of hormone combinations and levels (especially estradiol) to produce a safer next generation of OCs. Recent developments in oral and nonoral contraceptives have provided for new noncontraceptive benefits that not only will help women choose a method of contraception that is right for them but also may provide noncontraceptive health and lifestyle benefits that may encourage compliance.

The development and availability of OCs are a topic rich in controversy (religious, political, social, etc.); however, the primary purpose of this retrospective is to look beyond controversies and examine the past 50 years of the pill, focusing on the science behind the OC, the health-related stumbling
blocks that led to modifications of the original pill, the discovery of benefits beyond contraception, and a look into the future of contraception beyond the pill. These sections were contributed by presenters in a symposium entitled “50 Years of ‘the Pill’: Risk Reduction and Discovery of Benefits Beyond Contraception” sponsored by the Women In Toxicology Special Interest Group at the Society of Toxicology 50th annual meeting held from 6 to 10 March 2011 in Washington, DC.

A BRIEF HISTORY

Contraceptive control using medical devices has appeared throughout history, beginning with Egyptian documents circa 1500 BC that instruct women on how to mix dates, gum Arabic, and honey smeared on wool to serve as a contraceptive agent (http://www.time.com/time/printout/0,8816,1983970,00.html). Casanova’s diaries from the 1700s described his experiments with sheepskin bladder condoms and a half lemon as a makeshift cervical cap. In 1873, the U.S. Congress deemed birth control information obscene and outlawed its dissemination. However, in spite of these restrictions, an early version of the diaphragm became available in the 1880s. A groundswell effort began in the 1920s with Margaret Sanger’s founding of the American Birth Control League, which later became Planned Parenthood Federation of America (Calaf and Alsina, 2010; Dhont, 2010; Williams and Stancel, 1996; http://www.pbs.org/wgbh/amex/pill/index.html). Prompted by Sanger, Drs Gregory Pincus and John Rock began research and testing on the use of hormone contraception. In the 1930’s, it was discovered that temporary sterility could be induced when the ovaries of pregnant animals were transplanted into nonpregnant animals. The active agent producing an antiovulatory effect was identified as progesterone. Further experiments were enabled by extracting progesterone from animal ovaries until it was discovered that progesterone could be manufactured from diosgenin, which was extracted from a Mexican yam. However, poor oral bioavailability limited the use of progesterone monotherapy as a contraceptive agent until Dr Carl Djerassi developed synthetic orally active progesterone called “progestin” (norethindrone, followed by norethynodrel, a close isomer of norethindrone) in the 1950s. Clinical trials were conducted in Puerto Rico because dispensing contraceptives was still a criminal offense in the United States. These trials indicated that synthetic estrogen in combination with progestin was effective as a contraceptive and was only associated with minimal breakthrough bleeding.

In 1957, the FDA approved Enovid 5 (10 mg norethynodrel plus 0.15 mg mestranol) for menstrual disorders and extended the indication to include contraception in 1960. In 1961, G.D. Searle and Co. marketed Enovid 5 as an OC (Dhont, 2010). THE SCIENCE BEHIND HORMONAL CONTRACEPTIVES

It is notable that hormonal contraceptives are among the most effective drugs available, with 99.9% theoretical effectiveness (actual effectiveness is influenced by correct usage by the patient). The menstrual cycle is a complex series of events orchestrated by estrogen and progesterone (Williams and Stancel, 1996; http://www.pbs.org/wgbh/amex/pill/index.html). During a normal cycle, low levels of estrogen in the early part of the cycle signal the pituitary gland to release follicle-stimulating hormone (FSH), which promotes maturation of a dominant follicle in the ovary (the follicle consists of the egg and the estrogen-producing cells that surround the egg). As estrogen levels rise, the endometrium thickens and a massive luteinizing hormone (LH) surge triggers ovulation, where the mature follicle bursts releasing a mature egg to travel down the fallopian tube. The ruptured follicle is transformed into the corpus luteum, which produces progesterone. Progesterone is the dominant sex hormone in the second half of the menstrual cycle and makes the thickened endometrium favorable for implantation. Progesterone also signals back to the pituitary to suppress FSH and LH, ensuring that no additional follicles mature and are released. If the egg is not fertilized by the sperm, the corpus luteum regresses and the levels of estrogen and progesterone fall. The endometrial lining breaks down and is released at menstruation with the cycle beginning again. If the egg becomes fertilized and the resulting embryo implants, production of progesterone continues due to rescue of the corpus luteum by human chorionic gonadotropin, which is produced by the implanting embryo. Progesterone production is then over by the placenta, preventing the maturation of any additional eggs in favor of the developing fetus.

When a woman is on a hormonal contraceptive, the synthetic estrogen suppresses the production of FSH in the pituitary, preventing follicle maturation. Without a developing follicle, there is no increase in estrogen and the endometrium does not thicken. In constant, low-level progesterone makes the endometrium inhospitable for implantation of an embryo and also prevents the LH surge, preventing ovulation. Continued delivery of estrogen and progesterone throughout the cycle maintains the suppression of FSH and LH, preventing opportunity for pregnancy. During the 7-day placebo period that typically follows 21 days of hormone in many formulations, the absence of exogenous estrogen and progesterone allow for the breakdown and release of the thin endometrial lining as a withdrawal bleed, similar to menstruation.

SAFETY CONCERNS AND REFINEMENT OF “THE PILL”

From a medical perspective, the idea of medicating a patient who did not have a disease was a novel concept. In this case, the typical patient population would be young and healthy women, making the side effect profile, including long-term safety of the medication especially important. In the case of
“the pill,” early concerns about cancer due to the growth-promoting effects of estrogen led to the testing of progestin-only pills (Burkman, 2004; Dhont, 2010; Williams and Stancel, 1996). However, it was discovered that a small amount of estrogen (mestranol) together with progestin prevented ovulation more consistently and was associated with less breakthrough bleeding. Enovid was a combination of estrogen/progesterin preparation. In fact, most contemporary OCs are either estrogen/progesterone combinations or progestin-only preparations. Concerns about estrogen and the possibility of cancer remained heightened with the availability of “sequential” OCs between 1965 and 1970. Sequential OCs provided estrogen for 14 days followed by an estrogen/progesterone combination for 7 days. Reports of endometrial pathology and questions about the efficacy of sequential OCs led to their withdrawal from the market. In parallel, the levels of hormones in OCs, especially estrogen, were reduced while maintaining contraceptive efficacy in an attempt to reduce concerns about the potential for causing cancer. Current data do not indicate a strong correlation between OCs and increases in cancer. There is a small increased risk of breast and liver cancer, but the data are confounded by the use of older high-estrogen preparations (Burkman, 2004; Dhont, 2010; Williams and Stancel, 1996). Longer experience with the low-estrogen preparations will hopefully provide some clarity. In contrast to the suspected risk of cancer with OCs, there is good evidence for OCs reducing the risk of ovarian, endometrial, and possibly colorectal cancer.

Besides cancer, an increased risk for thromboembolism was another challenge faced by OC users (Burkman, 2004; Dhont, 2010; Williams and Stancel, 1996). The concern is based on the ability of estrogen to promote synthesis and thus increase the levels of multiple clotting factors, which is discussed in a subsequent section. There are data that demonstrate an increased susceptibility to thromboembolism in OC users compared with nonusers. Again, the reduction in estrogen in newer preparations has helped to reduce the incidence of prothrombotic and prohypertensive side effects.

**BEFORE THE 21/7-DAY REGIMEN**

Aside from pregnancy prevention, there are numerous other benefits associated with taking “the pill” (Burkman, 2004; Dhont, 2010; Williams and Stancel, 1996). These benefits include cycle regularity and decreases in blood loss, iron deficiency anemia, and dysmenorrhea. A reduction in acne, functional ovarian cysts, benign breast disease, the chance of ectopic pregnancy, and protection against some cancers is also seen. Emerging evidence suggests that “the pill” may have metabolic benefits, including positive effects on bone mass and prevention of endometriosis and pelvic inflammatory disease (Williams and Stancel, 1996). Finally, a recent study that tracked users and nonusers for up to 39 years suggested that “the pill” is not associated with an increased long-term risk of death, but may in fact produce a net longevity benefit (Hannaford et al., 2010).

**BEYOND THE 21/7-DAY REGIMEN**

The right frequency of a menstrual cycle while on OCs has been a source of much debate (Dhont, 2010; Williams and Stancel, 1996). The traditional OC regimen of 21 days of hormones followed by 7 days of placebo was influenced by society and culture, which suggested that menstruation every 28 days was a sign of normal female reproductive function. Others cite the lifestyle benefit of being able to control menstrual timing that could also result in less frequent menstrual symptoms and endometriosis pain.

Although FDA only approved an extended regimen OC in 2003, the off-label practice of extended use has been occurring for many years. Available options include a shorter hormone-free interval (2–4 days instead of 7 days) and extended hormone regimens (3 months on hormones followed by a 7-day hormone-free interval or 12 months on hormones with no hormone-free interval).

**RISK REDUCTION**

**Venous Thromboembolism**

Soon after the introduction of combined oral contraceptives (COCs), containing estrogen and progestin in 1960, the first case reports linking deep vein thrombosis (VTE) and pulmonary thromboembolism with COC use appeared in the literature. These initial cases of VTE were the impetus to lower the estrogen dose in an effort to reduce the VTE rate associated with COC use. Although risk remains for VTE even with lower amounts of estrogen in “the pill,” studies suggest a dose-dependent decrease in VTE risk when estrogen is reduced from 100 to 50 μg or lower (Lidegaard et al., 2002; Vessey et al., 1986). For example, a pharmacy-based study demonstrated a dose-response effect of VTE ranging from 10 events per 10,000 woman-years for greater than 50 μg estrogen pills to 4.2 events per 10,000 woman-years for less than 50 μg estrogen pills (Gerstman et al., 1991). Limited understanding evolved regarding OC components or dosages until studies published in late 1995 and early 1996 suggested that two of the newer progestins, gestodene and desogestrel, carried a higher risk for VTE than older progestins, such as levonorgestrel (CCDC, 1999; World Health Organization Working Group [WHO-WG], 1998).

Current low-dose COCs roughly triple the VTE risk compared with those not using OCs, though some studies with formulations containing gestodene or desogestrel have shown a sevenfold increased risk compared with nonusers of OCs. These findings are controversial, with concerns being raised about possible sources of statistical bias and lack of
biologic plausibility (Lewis, 1998). For example, prescription bias favoring use of newer COCs in all women including those at higher risk of VTE, such as first time users of COCs or inadequate comparisons of COC users with varying durations, and patterns of pill use (Corson, 1996; Suissa et al., 1997). One comprehensive analysis of VTE risk among low-dose COC users determined no difference in the risk of VTE among repeat users of COCs containing the older versus the newer progestins, following adjustment for a number of confounding factors (Suissa et al., 2000). In addition, the VTE risk was similar among those changing their method of oral contraception, either from older to newer COCs or from newer to older COCs. A few subsequent studies demonstrated an increased risk of VTE associated with COCs containing progestins, desogestrel, and drospirenone compared with those containing levonorgestrel, although there are concerns regarding the adequacy of the study designs (Dunn, 2011; Jick and Hernandez, 2011; Jick et al., 2006; Parkin et al., 2011).

It should be noted that the mortality due to VTE among COC users is quite low. However, age does affect mortality; for women aged 35–44 years, the mortality rates double compared with those in their 20s. Obesity and age were also risk factors for VTE among COC users, although the former is not a consistent finding in all studies (CCCC, 1999; Pomp et al., 2007; WHO-WG, 1998). Other factors suspected to enhance VTE risk among users of COCs included smoking or the presence of varicose veins, but these were ultimately excluded. The identification of the factor V Leiden mutation in 1993 introduced another consideration about the relationship between COC use and VTE. This mutation results in a variant of factor V resistant to activated protein C, which leads to enhancement of clot formation and an increased risk of VTE. Also known as activated protein C resistance, this mutation has a prevalence of about 5% in American Caucasian women, 2.2% in Hispanic Americans, and 1.2% in African Americans, making it the most commonly occurring natural anticoagulant deficiency (Vandenbroucke et al., 1994; Winkler, 1998). With the mutation at a prevalence of about 5% (Vandenbroucke et al., 1994), the risk for reproductive-aged women with the mutation who were not using COCs was 5.7 VTE events per 10,000 woman-years. In contrast, among COC users with the mutation, the rate increased to 28.5 events per 10,000 woman-years. Thus, the absolute risk of VTE among such women is considered quite low. One investigator determined that screening 1 million potential COC users for all known coagulation factor deficiencies or mutations not only would identify about 50 women at risk but also would result in about 62,000 women having false-positive results (WHO Study—Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996).

**Stroke**

Stroke is often classified as ischemic, thrombotic, or hemorrhagic. Although estrogen dose is important, several studies evaluating the risk of stroke events among users of COCs have better recognized the role of confounders and have used more rigorous approaches to both design and analysis (Schwartz et al., 1998).

**Ischemic Stroke**

The absolute risk of thrombotic or ischemic stroke among current users of low-dose COCs appears to be relatively low, even though the relative risk may be elevated for some women (WHO Study—Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996). For example, among women aged 20–24 years, the overall risk among COC users is increased by about 2.5 times compared with nonusers, but the absolute risk in both groups is very low (CCCC, 1999). There is no evidence that the type of progestin influences risk or mortality associated with ischemic stroke (CCCC, 1999). However, the risk of ischemic stroke does appear to be directly proportional to estrogen dose (WHO-WG, 1998). Age appears to be a risk factor relatively independent of COC use, with the relative risk of ischemic stroke doubling as women reach ages 40–44 years compared with users in their 20s. Hypertension, cigarette smoking, and migraine headaches also substantially increase the risk of ischemic stroke with COC use (WHO-WG, 1998).

**Hemorrhagic Stroke**

Age independently increases the risk of hemorrhagic stroke in both COC users and nonusers. The components of COCs, their dosages, and duration of use do not affect the risk of hemorrhagic stroke. The risk of hemorrhagic stroke in young women is low and not increased by use of COCs unless other risk factors are present (CCCC, 1999; Petitti et al., 1996; WHO-WG, 1998). In addition to age, the major risk factors for hemorrhagic stroke are cigarette smoking and hypertension (Petitti et al., 1996). Smoking, compared with nonsmoking, increases the risk of hemorrhagic stroke about twofold among non-oral contraceptive users and at least threefold among COC users (WHO-WG, 1998). With current COC use, in the absence of hypertension, the risk of hemorrhagic stroke is not elevated, but with a history of hypertension, the relative risk among COC users rises to as high as 10.2–14.2 (WHO Study—Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception, 1996; WHO-WG, 1998). Overall, for women less than 35 years of age who do not smoke and who are normotensive, the risk of hemorrhagic stroke is not affected by COC use (CCCC, 1999).

**Myocardial Infarction**

Increasing age and smoking are major determinants for the risk of myocardial infarction (MI) and other forms of ischemic heart disease. Thus, research indicates that COC use is associated with an increased risk of MI, particularly in women who smoke and are over the age of 35 years, including those who have underlying risk factors for coronary-artery disease, such as hypertension (Croft and Hannaford, 1989). Findings
from several early case-control studies suggested that the risk of MI was two to four times greater in women who currently used COCs than in nonusers (Mann and Inman, 1975; Mann et al., 1975). Several studies have confirmed the substantial increase in MI risk in pill users who smoke, as well as contraceptive pill users who have hypertension (Goldbaum et al., 1987; Rosenberg et al., 1985). Most of the MI risk related to COCs is attributed to their use in smokers over 35 years of age; the risk of MI is not increased with COC use in nonsmoking women without cardiovascular risk factors, such as hypertension.

The progestin contained in COCs may also affect the risk for MI. One group noted an increased risk with use of levonorgestrel-containing COCs but no significant increased risk with desogestrel- or gestodene-containing COCs when compared with nonusers (Tanis et al., 2001). In a meta-analysis of seven studies evaluating the MI risk associated with formulations containing less than 50 μg of ethinyl estradiol plus norgestrel or levonorgestrel versus preparations containing desogestrel or gestodene, the odds ratio for MI among COC users containing norgestrel or levonorgestrel was 2.2 (95% confidence interval [CI] 1.62–2.94), compared with an odds ratio of 1.1 (95% CI 0.67–1.9) for the second group with both groups being compared with nonusers (Spitzer et al., 2002).

In summary, use of current COCs is associated with a low attributable risk of VTE and to a limited extent with increased risk of stroke and MI. Although there are substantial data on this subject, clinicians must always bear in mind that pregnancy, the condition COCs are designed to prevent, in general carries a substantially higher risk for these disorders.

OTHER METHODS OF CONTRACEPTION AND THE FUTURE

Emergency Contraception

Emergency contraception is an approach to prevent pregnancy after unprotected intercourse or with known failure of a contraceptive method, such as a leaking condom. The major methods used for emergency contraception include high-dose COCs containing the progestin levonorgestrel, levonorgestrel tablets, and ulipristal acetate. These methods prevent pregnancy by delaying or inhibiting ovulation or by disrupting the function of the corpus luteum. To be effective, COCs must be taken within 72 h of intercourse, whereas the other two methods may be effective up to 5 days after intercourse. Emergency contraception, if used appropriately, can reduce the risk of unintended pregnancy by as much as 60–75% (American College of Obstetricians and Gynecologists, 2010).

Female Contraception

In the past 50 years, tremendous progress has been made in biomedical sciences and pharmaceutical technology. However, few advances other than “the pill” have impacted the lifestyles of so many. To date, development of contraceptives has exploited manipulation of biological molecules inherent to reproduction. This has led to considerable success for contraceptive interference with hormone-mediated pathways leading to gamete production (sperm and eggs) and/or reproductive behavior. The knowledge of the female reproductive process from oogenesis to implantation has a direct effect on contraceptive strategies. Because hormonal contraception is widely accepted and has a low failure rate, continued research has explored and introduced new formulations and combinations (estrogen + progesterone or progestogen only) as described by Li and Anderson (2010).

Gonadotropin-releasing hormone (GnRH) has received considerable attention in the last 15 years, given its ability to disrupt follicular maturation and ovulation. Produced in the hypothalamus, GnRH is secreted in a pulsatory manner to stimulate LH and FSH release from the pituitary. Many potent agonists and antagonists have been developed (Natraj, 2001). Agonists work in a biphasic manner, first stimulating and ultimately inhibiting the release of GnRH. Antagonists, on the other hand, act by blocking the receptor. However, because of their peptide structure, existing GnRH agonists/antagonists are injectable and not orally active. A new generation of nonpeptide GnRH “mimics” are in development, with the advantages of being nonpeptide, having a small molecule structure with high affinity for the receptor (Betz et al., 2008), and being orally active (Struthers, 2005). GnRH mimetics must navigate a balance of pituitary suppression with oral administration that is simply not available with downregulating agonists or one-size-fits-all antagonists. Currently, no GnRH mimic contraceptives have advanced to the market.

Long-acting reversible contraceptives (LARCs), like implants and intrauterine drug delivery products (IUDs), are the most effective reversible contraceptives. The major advantages of LARCs are that they do not require too much effort on the part of the user, they are very effective, and the return to fertility is rapid after the removal of the device. IUDs are the second most widely used contraceptives, following sterilization in the less developed regions of the globe (Anderson and Baird, 2002). IUDs can interfere with sperm transport and prevent fertilization and/or embryo implantation in the uterus. Many different types of IUDs are in the market, including a levonorgestrel-releasing IUD. The first single-rod contraceptive implant was approved by the FDA in 2006. Since then, millions of women worldwide have used this method of contraception. The primary mechanism of action is suppression of ovulation by altering the hypothalamic-pituitary-ovarian axis. The implant is a very successful method of contraception, with a pregnancy rate of only 0.05% (American College of Obstetricians and Gynecologists, 2011).

Male Contraception

The male reproductive system offers a range of potential targets for new contraceptives (Anderson and Baird, 2002). From a therapeutic standpoint, male contraception has historically been considered less viable than female contraception, given that spermatogenesis is a continuous process, involving daily production of millions of sperm. Spermatogenesis is regulated
CONCLUSIONS

The availability of hormonal contraception in the form of “the pill” in the early 1960’s was controversial and sparked endless social debate that still exists in some circles 50 years later. However, its acceptability can be clearly demonstrated by the fact that nearly 200 million women worldwide are using “the pill.” Hormonal contraceptives provide freedom from unwanted pregnancy and associated economic burden, opportunity to determine the time and number of pregnancies, a reduction in pregnancy-associated health risks, and diminished risk for certain forms of cancer. Safety concerns arising with early versions of “the pill” ultimately resulted in improvements in safety and efficacy, as evidenced in longitudinal studies that have demonstrated benefits beyond contraception.

The next generation of contraceptives will be based on the identification of novel molecules essential for reproductive processes. Identification of the genes responsible for fertility/infertility and the reproductive process, and pathway in which these genes function, will advance the fields of reproduction/fertility research. Importantly, this has potential to reveal novel human contraceptive targets. Recent scientific and technological advances in genomics, proteomics, new materials, and new drug delivery systems, along with a new understanding of reproductive biology offer the promise of new, safe, and effective forms of contraception. These new forms of contraception include novel approaches to male contraception that requires identification of previously unknown proteins critical for male reproduction. Alternatives to “the pill,” such as contraceptive eluting patches, implanted devices, and modulating the frequency of menstruation with OCs are emerging. Research in these areas would facilitate novel approaches for contraception using new technologies to address important unmet needs for women seeking an efficacious, safe, and convenient method of contraception.

Given the evolution of “the pill” over the past 50 years, challenging both pharmacological and societal barriers, it will be interesting to see what changes the next 50 years will hold for “the pill.”

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