



# The Role of Contraception in the Past, Present and Future

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## **Abstract**

*Contraceptives play an undeniable important role in woman's lives. It is widely accepted that the availability of both hormonal and non-hormonal modern contraceptives have improved women's lives worldwide by allowing women to control their own fertility. Indirectly, contraceptives have been shown to reduce maternal mortality, unwanted pregnancy, and overpopulation. However, the contraceptives available today may not be suitable for all users. Furthermore, there is still need to expand available current contraceptives choices especially long-term contraceptives in order to improve acceptability. As a result, several novel products such as implants, contraceptive vaginal rings, and transdermal patches have recently been introduced in family planning programs. Additional issue of contraceptive needed to be addressed is the adverse effects of hormonal contraceptives. Therefore, new combinations with an improved metabolic profile is currently being researched. Generally, the introduction of new methods with additional health benefits and less side effects would help women with their unmet needs to obtain access to a wider range of contraceptives.*

**Keywords:** *Contraception; progestins; estrogen; intrauterine system; thrombosis*

## Peranan Kontrasepsi Dahulu, Sekarang dan Masa Depan

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### Abstrak

Kontrasepsi memainkan peranan penting dalam kehidupan wanita. Sudah diterima secara luas bahwa ketersediaan kontrasepsi modern hormonal dan non-hormonal telah meningkatkan kehidupan wanita di seluruh dunia dengan memungkinkan seorang perempuan untuk mengontrol fertilitasnya. Secara tidak langsung, kontrasepsi telah terbukti mengurangi angka kematian ibu, kehamilan yang tidak diinginkan, dan kelebihan penduduk. Namun, kontrasepsi yang tersedia saat ini mungkin tidak cocok untuk semua pengguna. Selain itu, masih perlu memperluas pilihan kontrasepsi saat ini yang tersedia terutama kontrasepsi jangka panjang untuk meningkatkan akseptabilitas. Akibatnya, beberapa produk baru seperti implan, cincin vagina kontrasepsi, dan patch transdermal baru-baru ini diperkenalkan dalam program keluarga berencana. Masalah tambahan kontrasepsi yang perlu ditangani adalah efek samping dari kontrasepsi hormonal. Oleh karena itu, kombinasi baru dengan profil metabolik yang ditingkatkan saat ini sedang diteliti. Umumnya, pengenalan metode baru dengan tambahan manfaat kesehatan dan lebih sedikit efek samping akan membantu wanita dengan kebutuhannya yang belum terpenuhi untuk mendapatkan akses kontrasepsi yang lebih baik.

**Kata kunci:** Kontrasepsi; progestin; estrogen; system intrauterin; trombosis

## Introduction

It is stated in Millennium Development Goals (MDGs) that universal access to reproductive health must be available in any given society. The reproductive health stated in MDGs involves access to important reproductive health services including contraceptive options, safe abortion, maternal mortality reduction (MDG 5), and gender equity (MDG 3). The accessibility and usage of hormonal contraception for limiting births in developing countries has been shown to be increasing since 1960s.<sup>1</sup> However, most of the methods available which are not long-acting are often discontinued within 8 months of first use due to fear of side effects and lack of access to renewed prescription.<sup>1,2</sup> Several other factors also contribute to the problem such as safety misperceptions, lack of knowledge, low acceptability of contraceptive methods, low compliance, and cultural factors.<sup>1-3</sup>

It is reported that 63% of reproductive age group women in the world use contraception.<sup>2</sup> The contraceptive prevalence in developed countries remains unchanged while a significant increase of contraceptive use in developing countries starting from 1990s is reported.<sup>2</sup> Together, oral contraceptive (OC) pill for women and condom for men, account for almost 50% of overall contraceptive use in developed countries. Meanwhile, in developing countries, female sterilization and intrauterine devices (IUD), account for 60% of overall contraceptive use.<sup>4</sup>

## Contraceptives and Welfare

In an article published in the *Lancet*, Cleland and colleagues wrote “Contraception is unique among medical interventions in the breadth of its positive effect on health.” Contraception has saved millions of lives. It is estimated that increased contraceptive use has cut the number of maternal deaths in developing countries by about 40% since the mid-1990s. Preventing unintended pregnancy among women at risk of poor obstetric outcome—the very young, the very old, and the highly parous—prevents additional deaths. Prevention of induced abortion is vital in reducing maternal mortality and morbidity in countries where abortion is illegal and/or unsafe. By increasing interpregnancy intervals, contraception also saves the lives of countless children and improves their overall health. In the developed world, contraception has emancipated women, allowing them to choose whether and when to have children, and allowing them to play an equal role in society.<sup>5-7</sup>

The non-contraceptive benefits of modern methods improve quality of life for many individual women and contribute to improved public health in, for example, cancer prevention. Disappointingly, in many countries, including the United States and the United Kingdom, unintended pregnancy rates are high despite good contraceptive prevalence.<sup>8-10</sup>

Contraceptive prevalence has increased dramatically since the mid-1960s. In 2011, 63% of women aged 15 to 49

married or in a union were using contraception (all methods) and 56% were using modern methods, resulting in a world total fertility rate (TFR) of 2.4 (TFR represents the number of children that would be born to a woman if she were to live to the end of her childbearing years and would bear children in accordance with current age-specific fertility rates). These impressive statistics, hide enormous variation between countries. In the United Kingdom, 84% of married women use contraception, whereas in Chad only 3% are using any method. In the United States in 2009, the TFR was 1.9, which is well below the rate of 2.1 at which, without immigration, population growth stops. Demographic change has an impact on contraceptive use. The average age of first intercourse has fallen (in the United Kingdom, it has stabilized for both men and women at 16 years), and the average age of first childbirth has risen to almost 30 in many developed countries. Thus many women spend years trying to avoid conception.<sup>5,7,11</sup>

Patterns of contraceptive use vary across the world, and choice of contraceptive method depends on numerous factors. In the United States, the most common methods used are the pills (28%) and female sterilization (27%). Use of intrauterine devices (IUD) has increased since 1995 (from 0.8% in 1995 to 5.6% in 2006 through 2010), probably as a result of the increased use of the hormone-releasing IUD. On the other hand, fewer women report that their partners are using condoms as their current, most effective contraceptive method. In contrast, for example, sterilization is much *less* common and IUD use much *more* common in France and Sweden, and many more women in France use the pill compared with women in either the United States or Sweden. Globally, the most common methods used are female sterilization (38%), IUD (25%), and combined oral contraceptives (COCs) (7.5%).<sup>7,10,11</sup>

Not only do patterns of contraceptive use vary among countries, but they also vary in the same country between different age groups and stages of life. Contraceptive use also varies according to ethnicity and race, marital status and fertility intentions, education, and income. Despite the high prevalence of the use of contraception, unintended pregnancy is common and so is induced abortion. Although much of the decline in population growth has been achieved through contraceptive use, no country has achieved low fertility rates without access to abortion. In the United States, the abortion rate in 2008 was 19.6/1000 women of reproductive age (compared with around 15 in England and only 5 in the Netherlands), despite apparently widespread use of contraception. In an impressive national survey of 10,683 U.S. women having an abortion in 2000 and 2001, 54% claimed to be using contraception in the month of conception: 28% condoms and 14% the pill. Women who were not using a method at the time of conception (46%) perceived themselves at low risk of pregnancy (33%), had experienced problems with contraception in the past, or had concerns about

side effects (32%).<sup>3,4</sup>

### **History of Oral Hormonal Contraceptives**

Oral contraceptive pill is currently the most popular form of contraception used worldwide with around 100 million women as current users.<sup>12,13</sup> Historically, the first generation steroidal OC pill for public use was approved in the 1961 with either mestranol or ethinylestradiol (EE) as its component.<sup>2,13</sup> Its creation marked the start of a new era as women had the possibility and means to control their fertility. Hence, OC pill was quickly adopted by a huge number of women rapidly.<sup>13</sup> Other factors also contribute to the rising popularity of OC pill such as easy of use, reliability, and sense of empowerment.<sup>2,13</sup> However, less than 10 years after OCs introduction to the public, concerns over the adverse effects arose, especially cardiovascular and neoplastic effects in OC pill users from estrogen reported by epidemiological studies.<sup>2,14,15</sup>

These side effects, although rare in the young population of OC users, were widely publicized in the media causing a decline in OC pill use. Since the side effects are related to the dose of estrogen, reduction to the initial EE doses in OC pill was made.<sup>13</sup> What was as high as 150 ig EE per pill was subsequently decreased to 100, 80, and 50 ig.<sup>2</sup> Later on, the EE dose of 50 ig was then decreased again to 15-30 ig in modern OC pills.<sup>2,13</sup> Due to lower doses of EE in currently marketed OC pills, there is significant reduction of venous thrombosis and cardiovascular risk when compared with previous OC pills.<sup>6</sup>

Early generation progestins used for OC pills had chemical structure related with testosterone.<sup>2</sup> As a result of this chemical similarity, unwanted androgenic side effects may occur in users such as oily skin, hair growth, lipid problem, and acne. A method to prevent the androgenic side effects is to produce new progestins derived from progesterone structure or from spironolactone.<sup>2,16,17</sup> Example of this new progestins are rospirenone (DRSP), dienogest (DNG), trimegestone (TMG), Nestorone® (NES) and nomegestrol acetate (NOMAc).<sup>16</sup>

Progestogen only pills such as levonorgestrel 30 ig, norethisterone 350 ig, and desogestrel 75 ig did not increase the risk of venous thromboembolism.<sup>2,15</sup> However, new progestins when combined with EE did not give better result in venous thromboembolism risk and actually may increase this risk when compared with Levonorgestrel (LNG) containing OCs.<sup>2,18</sup> Hence, the strategy to reduce venous thromboembolism risk in EE OC pills is to change the type of estrogen used with natural compounds such as estradiol (E2) and estradiol valerate (E2V). Currently, there are many large cohort studies ongoing that aim to determine whether the use of natural estrogen can decrease incidence of venous thromboembolism.<sup>8</sup>

### **Mechanism of Progestin Contraceptives**

The main mechanism of progestin contraception is by

thickening the cervical mucous, therefore preventing sperm movement and viability. Progestin also works by reducing Follicle Stimulating Hormone (FSH) and Luteinizing Hormone (LH) secretion. As such, LH surge can be depressed and subsequent ovulation is inhibited. However, the effect of progestin on ovulation inhibition is dose-dependent. Very low dose progestin contraception such as subdermal implant Norplant and intrauterine system Mirena are unable to inhibit ovulation consistently and therefore has to rely mainly on its mechanism of cervical mucous thickening to prevent pregnancy. Meanwhile, both intermediate and high dose progestin are able to inhibit ovulation consistently. Additional benefit of using high dose progestin is complete follicular development inhibition. Endometrium thinning occurs due to levonorgestrel and other synthetic progestin inhibiting progesterone receptor.<sup>6,9,11</sup>

### **Mechanism of Combined Hormonal Contraceptives**

Combined hormonal contraceptives contain both an estrogen and a progestin that inhibit both follicle development and ovulation. Most combined oral hormonal contraceptives are taken every day for three weeks and there is 7-day break with placebo pills allowing the resumption of follicular growth. However, the resumption of follicular growth may continue to ovulation if the contraceptive method is restarted late.<sup>3,7,19</sup>

### **Subdermal Implants**

Subdermal implants were first introduced in the United States in 1991. Previously, it was developed by The Population Council, an international organization founded in 1952 with the purpose of advancing contraceptive technologies. Implants works by providing slow sustained release of progestin subdermally. The hormone then causes anovulation, endometrial thinning, and cervical mucus thickening. Norplant is a hormonal implant composed of six capsules with each capsule has 34 mm length and 2,4 mm diameter. In total, Norplant contains 216 mg of Levonorgestrel. Studies have shown that after five years, there is still around 50% of active levonorgestrel in the capsules.<sup>9,10</sup>

Norplant II has two capsules and its use has been approved in Europe, Asia, and Africa. Norplant II uses 150 mg of levonorgestrel with each capsule having 43 mm of length and 2.5 mm of diameter. Implanon contains etonogestrel which has lower androgenic effect but higher progestational effect than levonorgestrel.<sup>3,9</sup>

Implants containing non-androgenic progestins such as Nestorone® (NES) or Nomegestrol acetate have shown potential interest but their development has been on hold due to insufficient funds. The advantage of Nestorone implants in the postpartum period would be high since the progestin secreted in breastmilk is not active orally, destroyed quickly after oral ingestion, and any small amount

ingested by the infant through the mother's milk will be inactivated rapidly. No effect of NES on lactation and infant growth was discovered and no serious adverse events were observed in the long-term study comparing the NES implant to the T-CuIUD.<sup>11</sup>

### **Injectables**

Hormonal injectables use norethisterone enanthate (NET-EN) and depot medroxyprogesterone acetate (DMPA) or Depo-Provera® that has been approved by the FDA since 1992. This form of contraceptive requires its user to take monthly injections to increase compliance.<sup>2</sup>

Side effects of injectables are similar with hormonal contraceptive.<sup>10</sup> However, there has been an association of using injectable contraceptives of DMPA (without estrogen) with a potential lowering in bone mineral density in young women.<sup>10</sup> As a precaution, DMPA is recommended to be given in lower dose form with duration of 2 years in young women.<sup>2</sup>

### **Non-contraceptive Health Benefits of Contraceptives**

Several beneficial non-contraceptive effects of COCs can be utilized outside of pregnancy prevention. For example, blood loss reduction from COCs are effective enough that FDA approves its use for menstrual bleeding. Other example include the use of LNG-IUS for endometrial ablation/resection in menstrual bleeding.<sup>19</sup> Additionally, both COCs and LNG-IUS are effective in reducing dysmenorrhea, menstrual bleeding, acne, and premenstrual dysphoric disorder. Several cancer can be prevented by the use of OCs such as ovarian, endometrial and colorectal cancers.<sup>18,19</sup>

### **Safety Aspect of Hormonal Contraceptives**

The controversy of possible risk of cardiovascular events in the form of thrombosis and cancer in OC pill users exists since the early days of hormonal contraceptives. Even now, the controversy is still not disproved completely despite numerous studies on the safety of hormonal contraceptives have been published over the years.<sup>9</sup>

Many studies of OC pill safety led to different results. Some of the studies, mainly the prospective studies, showed no difference in cardiovascular risk associated with the use of hormonal contraceptive when compared to second generation pills containing levonorgestrel. Meanwhile, observational studies tend to show an increase in risk. In interpreting the result of these studies, several risk factors need to be accounted for. For example, several important risk factors, particularly obesity, sedentarily life style, previous cardiovascular events, and smoking history were actually not adjusted for in several of the observational studies, decreasing the validity of these studies.<sup>9,18</sup>

Cardiovascular events such as venous thromboembolism and stroke from hormonal contraceptives can be explained by the changes caused by hormonal contraceptives in a va-

riety of metabolic factors such as hemostatic variables, lipid profile, and carbohydrate metabolism. These changes will then cause an increase of procoagulant state with subsequent risk of thromboembolism.<sup>2</sup> There are several approaches available that can be implemented to prevent the cardiovascular adverse events such as reducing the amount of estrogen dose, using different type of estrogen, selecting newer progestins, new administration schedules, and alternative routes of delivery.<sup>9</sup>

### **Non-Oral Hormonal Contraceptives Vaginal rings**

Contraceptive vaginal ring (CVR) is a recently introduced novel hormonal contraceptive method. CVR is either considered as a once-a-month contraception method that works by releasing hormones daily to vagina after insertion.<sup>2</sup> The advantages of the ring are that CVR is a user-controlled method and has easy insertion method, not requiring medical professionals for insertion and removal. Therefore, CVR also increases compliance as daily attention is not required. Furthermore, no specific insertion location of the ring is required and one size is suitable for all women.<sup>13</sup>

The ring is composed of copolymer ethylene vinyl acetate with 2,7 mg of EE and 11,7 mg of etonogestrel (ENG) equally dispersed. Around 15 µg EE and 120 µg ENG are released daily into the vagina.<sup>2,20</sup> The hormones released are then rapidly absorbed by vaginal epithelium which then pass into the general circulation and achieve a steady state.<sup>21</sup> CVR works similar with OC pills by preventing follicular development and ovulation. After 3-weeks in, the woman removes the ring from the vagina for 1 week. During this 1-week ring-free period of CVR, withdrawal bleeding occurs.<sup>20</sup>

In terms of efficacy, CVR provides lower systemic estrogen exposure and good menstrual cycle control with comparable efficacy when compared to OC in several Randomized Controlled Trials (RCTs).<sup>21,22</sup> Although CVR has lower systemic EE exposure than OC, there is no significant difference in the incidence of estrogen-related adverse events in CVR users when compared with OC.<sup>21-23</sup> Meanwhile, due to vaginal route of administration, CVR is associated with leukorrhea, vaginal discomfort, and foreign body sensation.<sup>20</sup>

### **Intrauterine Devices (IUDs)**

Development of contraceptive devices in uterus was described as early as 1900s in scientific literature. However, birth control was considered a crime in many countries, leading to slow development of these devices. The development of contraceptive devices started again in the 1960s with intrauterine devices (IUD) composed of inert plastic. The discovery that adding copper to IUD improves contraceptive efficacy, led to smaller IUD with easier insertion. The popularity of IUD plummeted in 1970s due to a scandal from 1 specific IUD, the Dalkon Shield which was associated with septicemia.<sup>24</sup>

Modern IUD is consisted of two types, either containing copper or progestin.<sup>24,25</sup> Copper IUD works by inducing cytotoxic inflammatory reaction in the uterus that prevent fertilization.<sup>25</sup> Significant copper concentration is found in cervical mucus of copper IUD users.<sup>24,25</sup> The presence of copper in cervical mucous produces inhibitory effect on sperm motility.<sup>25</sup> Meanwhile, progestin IUD releases LNG at a slow steady rate of 20 µg/day and has demonstrated high contraceptive efficacy up to a duration of 5 years.<sup>2</sup> Intrauterine delivery of LNG causes atrophy of the glandular and surface epithelium.<sup>23,25</sup> Other effects from LNG is suppression of spiral artery formation and down regulation of sex steroid receptors.<sup>24,25</sup> Overall, the endometrium becomes thin and decidualized resulting in unsuitable environment for sperm survival and fertilization.<sup>25</sup>

IUD is one of the most popular long-acting contraceptive methods due to the advantages IUD provides. IUD is long-lasting, effective, reversible, and does not have any effects on breast milk. Additionally, IUD can be inserted at any time provided that the woman is not pregnant. However, LNG IUD takes 7 days after insertion to be effective while copper IUD produces immediate contraceptive effect. LNG IUD should be avoided in woman with unexplained vaginal bleeding.<sup>25</sup>

### **Future Contraception**

New contraceptive would include better mid-acting and long-acting reversible contraceptives (LARC); better methods for spacing births that can be used by breastfeeding women. We need to know that the fields of infertility and fertility intersect and should be collectively mined for contraceptive research and development. Finally we need to make innovative way to identify selective and druggable targets that will lead to new contraceptive modalities with fewer side effects and with non-contraceptive health benefits.<sup>2,5,20,23,25</sup>

While implants and IUD require a health provider for proper insertion and removal, vaginal rings and transdermal patches or gels have the benefit for women of being under their own control. A one-year vaginal ring reaching final stages of development, has the potential for high compliance as the woman will have her method available for one full year. Research on new steroids closer to natural hormones and new non-oral delivery systems will target a better safety of hormonal methods. Today's research on new contraceptives, targets not only the prevention of unwanted pregnancies, but also medical benefits to the users. Dual protection methods are being tested in the form of vaginal gels or rings delivering both a contraceptive and an agent active against sexual disease transmission. In addition, the potential of PRM, to prevent breast cell proliferation or the neuroprotective effects of P and NES are new areas of research supporting the development of new contraceptives with added health benefits.<sup>2,5,17,18,24</sup>

## Conclusion

Effective and easy to use contraception is one of the major breakthroughs in medical science. The use of contraception has resulted in reduction of unwanted pregnancy, illegal abortion, and childbirth. However, there are still several areas for improvement of present contraceptive methods especially in safety, duration, compliance, and acceptability.

Future contraceptive development would include better mid-acting and long-acting reversible contraceptives (LARC) that results in higher compliance in users. Therefore, long acting methods development that does not require daily compliance should be given high priority. Meanwhile, better safety of hormonal contraceptives by researching new forms of steroids and new non-oral delivery is also required. These objectives when accomplished will help achieve the goal of eliminating unwanted pregnancies, improve maternal and child health as stated from the MDG

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