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CONTRACEPTION TECHNOLOGY: PAST, PRESENT AND FUTURE

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Abstract

Steady progress in contraception research has been achieved over the past 50 years. Hormonal and non-hormonal modern contraceptives have improved women's lives by reducing different health conditions that contributed to considerable morbidity. However the contraceptives available today are not suitable to all users and the need to expand contraceptive choices still exists. Novel products such as new implants, contraceptive vaginal rings, transdermal patches and newer combinations of oral contraceptives have recently been introduced in family planning programs and hormonal contraception is widely used for spacing and limiting births. Concerns over the adverse effects of hormonal contraceptives have led to research and development of new combinations with improved metabolic profile. Recent developments include use of natural compounds such as estradiol (E2) and estradiol valerate (E2V) with the hope to decrease thrombotic risk, in combination with newer progestins derived from the progesterone structure or from spirolactone, in order to avoid the androgenic effects. Progesterone antagonists and progesterone receptor modulators are highly effective in blocking ovulation and preventing follicular rupture and are undergoing investigations in the form of oral pills and in semi long-acting delivery systems. Future developments also include the combination of a contraceptive with an antiretroviral agent for dual contraception and protection against sexually transmitted diseases, to be used before intercourse or on demand, as well as for continuous use in dual-protection rings. Alhough clinical trials of male contraception have reflected promising results, limited involvement of industry in that area of research has decreased the likelihood of having a male method available in the current decade. Development of non-hormonal methods are still at an early stage of research, with the identification of specific targets within the reproductive system in ovaries and testes, as well as interactions between spermatozoa and ova. It is hoped that the introduction of new methods with additional health benefits would help women and couples with unmet needs to obtain access to a wider range of contraceptives with improved acceptability.

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1. Introduction

Societies in both the developing and developed world suffer from unacceptably high rates of unintended and unwanted pregnancies, despite the availability of safe and effective forms of contraception. Despite the progress made in recent decades in fertility reduction in developing countries, up to 120 million (10–12%) married women in most regions and more than 24% in sub-Saharan Africa, continue to report an unmet need for contraception [1]. The Millennium Development Goals (MDG) target of universal access to reproductive health reaffirms the need for contraceptive options as well as access to other key reproductive health services, including safe abortion, to reduce maternal mortality (MDG 5) and achieve gender equity (MDG 3). Since its introduction in the 1960s, hormonal contraception has been increasingly accessible and widely used for both spacing and limiting births in developing countries. However, still, most methods which are not long-acting are discontinued within 8 months of first use, mostly because of lack of access to renewed prescription or fear of side effects. Indeed, factors that contribute to this problem include misperceptions about safety, knowledge, acceptability of methods, compliance, access and cultural factors.

Rapid population growth has significant individual, family, societal and environmental effects and contributes to, among other things, high maternal and infant mortality and morbidity in many developing countries. The ability to control fertility through the use of effective contraception is an essential component of preventive medicine, ideally resulting in planned pregnancies and optimal health. Contraceptive methods, based on a fundamental understanding of the processes of successful reproduction, are not only important for individuals and families, but play an essential part in population-regulation and deserve an important place in the science of reproductive medicine [2].

The past 50 years have witnessed a steady progress in contraception research, beginning with the first oral contraceptive (OC) pill in the 1960s and emerging technologies such as the contraceptive vaginal ring (CVR) and transdermal patch in recent years.

The International Committee for Contraception Research (ICCR) was established in 1970 by the Population Council and pioneered research for development of a number of effective contraceptive methods which have been used by millions of women worldwide. Most long-acting methods such as intrauterine contraception (IUC) with devices (IUD) such as Paragard®, the CopperT380A or medicated systems (IUS) such as Mirena®, or subdermal implants such as Norplant® and Jadelle®, and vaginal rings have been designed by the ICCR members and initially developed by the Population Council and its committee. Development was continued by private-public partnerships with industrial collaboration to ensure large scale manufacturing and worldwide distribution.

At the world level 63% of women in the reproductive age group are reported to be using contraception, for a total of 716 million women worldwide [3]. While developed regions have shown little change in their contraceptive prevalence since 1997, there has been a significant increase in contraceptive use in developing countries. However, sub-Saharan Africa has the lowest contraceptive use (22%) in the developing world [3]. The pill for women, and condom for men, account for almost 50% of overall contraceptive use in

developed countries, while in developing countries, female sterilization and intrauterine devices (IUD), account for 60% of overall contraceptive use [3].

Despite the availability of safe and effective forms of contraception and increasing contraceptive use, societies in both developing and developed countries encounter unacceptably high rates of unintended and unwanted pregnancies which contribute to population growth. It is projected that by the year 2050, the world population will reach 8.9 billion which is much higher than the current number of 7 billion reached on October 31, 2011 [4–5]. About 81 million unintended pregnancies occur worldwide each year [6–7]. In the United States, the annual number of unintended pregnancies is estimated to be 3.1 million [8], with an unintended pregnancy rate of 51 per 1,000 women aged 15–44 years [9]. By 2015, the number of unintended pregnancies is projected to rise to 92 million globally [10]. In developing countries, 19 million women are reported to resort to unsafe abortions each year that result in an increase in maternal mortality, one of the most dramatic consequences of unintended pregnancy [11].

The leading factors that contribute to unintended pregnancies include ‘an unmet need for family planning’ or ‘contraceptive failure’. Nearly 50% of unintended pregnancies occur in contraceptive users; however, only 10% of such pregnancies result from true method failure. This finding may be attributed to using a contraceptive method with adherence requirements resulting in incorrect and inconsistent use which accounts for 43% of the unintended pregnancies in the United States [12, 13]. Nearly 1 million unintended pregnancies occur in oral contraceptive (OC) users each year in the U.S. The “pill” being the most commonly used form of contraception, requires perfect compliance to be fully effective [8]. Less than 3% of women of reproductive age in the United States are reported to use a long-acting reversible method such as the IUD or an implant [14]. According to estimates from the 2002 National Survey of Family Growth (NSFG) in the United States, 12.4% of all episodes of contraceptive use ended with an unintended pregnancy within 12 months after initiation of use [15].

Therefore, there is a need to expand the currently available contraceptive choices. The contraceptives available today may not be acceptable to all users [16]. The development of better tolerated methods as well as long-acting systems are of particular importance where no daily attention is preferred, thus improving compliance. Novel products such as new implants, CVRs, transdermal patches and newer combinations of OCs were recently developed and are currently marketed [16, 17]. The presently available user-controlled methods could be further improved for better compliance. Introduction of new methods, with added health benefits could moreover enhance willingness to use contraceptives.

The donor community and more recently the Bill and Melinda Gates Foundation have assessed the landscape of existing methods and those in early or late development and envisioned support for research in specific areas. Methods that are mid-acting or long-acting, or to be used on demand, or to be used during lactation for better spacing of pregnancy, or those bringing dual benefits, in particular to prevent HIV transmission are the selected priorities. Accelerating contraception development and testing its acceptability in sub-Saharan Africa and South-East Asia, both regions with the highest unmet needs may result in a game change five to 10 years from now.

2. Female contraception

2.1. Oral Hormonal Contraceptives

The first steroidal OC pill was approved in the 1960s. Because of its ease of use and the sense of empowerment and freedom that it gave to its users, the popularity and use of the

pill steadily increased throughout the 1960s. However, concerns arose over the adverse effects, especially cardiovascular and neoplastic effects, although rare in the young population of OC users, but these were widely publicized leading to a decline in their use [18]. Ever since its introduction, considerable changes have taken place in the composition of OCs in terms of type and dose of both the estrogen and the progestin. The first generation OCs contained mestranol which was then replaced by ethinyl estradiol (EE) initially in doses as high as 150 mcg per pill, which decreased to 100, 80, and 50 μg. The initial EE dose of 50 mcg was then decreased to 30 and 20 μg. The lower doses of EE in currently marketed OCs lead to a significant decrease in venous thrombosis and cardiovascular risk.

Most progestins used in OCs of the first and second generation were chemically related to testosterone (19-nortestosterone derivatives; estrane and gonane groups). However, these progestins were responsible for undesirable androgenic side effects such as acne, oily skin, and hair growth, as well as negative effect on high-density lipoproteins (HDL). New progestins derived from the progesterone structure or from spironolactone have been developed to avoid the androgenic effects and to improve the safety profile [19]. However, their combination with EE did not result in a better safety profile in terms of venous risk and may have increased this risk as compared with LNG containing OCs. [20]. Therefore, the recent trend has been a change in the type of estrogen used wherein natural compounds such as estradiol (E2) and estradiol valerate (E2V) are being used with the objective of overcoming metabolic effects and decrease the thrombotic risk of formulations with EE. A recently approved four-phasic pill containing estradiol valerate (E2V) and dienogest has shown favorable results in hemostasis and metabolism studies [21], and similar favorable metabolic profile has been reported with a combination of E2 and nomegestrol acetate recently approved in Europe [22]. However, large safety surveillance studies are ongoing and will confirm whether the improved metabolic profile will correlate with a decreased incidence of VTE.

While traditional forms of OC included the 21 days of hormone-containing pills and 7 days of placebo during the hormone-free interval (HFI), the Food and Drug Administration (FDA) approved the 24/4, 84/7, and 365-day regimens in 2003. These changes have resulted in reduced risks of ovulation and an acceptable bleeding pattern.

2.2. New molecules for oral contraception with natural estrogens or without estrogen

An OC combination of 17β estradiol (1.5 mg) and nomegestrol acetate or NOMAc (2.5 mg); a 19-norprogesterone derivative recently approved in Europe, has shown high contraceptive efficacy and good bleeding control [23].

Another natural form of estrogen, estetrol (E4), which under physiological conditions is only produced during pregnancy by the liver of the fetus, has been synthesized. Formulations with E4 have been developed in combination with potent antigonadotropic progestins such as levonorgestrel (LNG) or etonogestrel (ENG). E4 was found to be 18 times less potent than EE, does not convert into other estrogens in the liver and is therefore predicted to produce less adverse effects [24].

Progesterone antagonists (PA) and progesterone receptor modulators (PRM), earlier known as selective PRM (SPRM), and ligands to the progesterone receptor (PR) are highly effective in blocking ovulation and preventing follicular rupture [25]. The concept of using a PRM as a contraceptive could be perceived favorably due to its endometrial action that leads to amenorrhea [26]. A Phase II study of CDB (VA)-2914 or Ulipristal acetate (UPA), delivered via the oral route at doses of 2.5 mg, 5 mg and 10 mg/d caused suppression of ovulation and amenorrhea in about 80% of women in the 2 higher dose groups [27]. Oral UPA has recently been approved for emergency contraception as a single oral dose of 30 mg

and appears to be effective for a longer duration, up to 5 days postcoital, than LNG emergency contraception active up to 3 days following a single act of unprotected intercourse [28]. The use of this molecule in long-acting delivery systems such as a vaginal ring appears promising and is currently being investigated [29].

2.3. Non Oral Hormonal Contraceptives

2.3.1. Vaginal rings: (see also chapter from Vivian Brache in this issue of the journal)—

The contraceptive vaginal ring (CVR) is a relatively new hormonal contraceptive method, considered a semi long-acting or mid-acting method. Hormones released from the CVR are rapidly absorbed by vaginal the vaginal epithelium, pass into the general circulation, achieve rapidly a steady state, and prevent follicular development and ovulation [30, 31]. The advantages of the ring, a user-controlled method, include its easy insertion and removal by the woman herself on a 3-weeks in, 1-week out schedule. The ring does not need to be placed in a specific site and one size is suitable for all women. Therefore the method is easy to distribute as it does not need trained health providers for insertion and removal, and also it may increase compliance as daily attention is not required.

A combined hormonal CVR NuvaRing®, which is a monthly ring delivering etonogestrel ENG (120 mcg/day) and EE (15 mcg/day) for 3 weeks is currently available and has been shown to have high acceptability and contraceptive efficacy with a Pearl index ranging from 0.25 to 1.75 per 100 woman-years [32–33].

Another 3-month ring which contains only natural progesterone (P) is marketed under the brand name Progering®, in Chile and Peru, and has been more recently approved for use by lactating women in several other countries of Latin America. This progesterone vaginal ring (PVR) is designed to release about 10 mg of P daily in order to prolong lactational amenorrhea (LAM) and can be used up to one year (4 rings of 3 months duration). It is highly effective as shown in various studies which found the annual pregnancy rate to range from 1.5 per 100 [34], to no pregnancy being reported [35], which is not different from the rate in IUD users. Its mechanism of action relates to the antigonadotropic action of P and also increases in the response of prolactin to suckling which inhibits the hypothalamic pituitary ovarian axis.

2.3.2. Other vaginal ring methods in clinical development—

The NES/EE one-year ring, used for a 3 week in, 1 week out schedule, releasing low doses of Nestorone® (NES) (150 mcg/d) and EE-(15 mcg/d) developed by the Population Council has completed Phase III trials. Nestorone is a potent 19 nor-progesterone derivative with no androgenic or estrogenic action that is inactive orally, but is highly effective to block ovulation when used by non oral routes [19].

A second-generation NES/E2 3-month vaginal ring delivering Nestorone with E2 is currently undergoing Phase II studies [Population Council and NICHD collaborative study, (Clinical Trials.gov Identifier: NCT01586000.]

A first dose-finding study with a 3-month ring delivering ulipristal acetate (UPA) (UPA-CVR), in doses on 600 to 800 mcg showed absorption of the PRM from the vagina, and in women whose serum levels reached 7 ng/mL or above, ovulation was suppressed but these serum levels were observed in only 68% of 78 cycles in the initial study [29]. Higher doses of UPA delivered via CVR have been evaluated in a second dose-finding study and preliminary results showed up to 90% suppression of ovulation (Population Council, data on file).

Dual rings: Several organizations are currently developing combination rings delivering an antiretroviral agent together with a contraceptive steroid (see below, methods with dual benefits)

2.3.2.1. Transdermal delivery systems: patches, gels, skin spray: Ortho EVRA® is a currently marketed contraceptive patch which consists of a matrix system that releases the progestin norelgestromin (150 mcg/day) and EE (20 mcg/day) for a 7-day patch. The patches are used for 3 weeks followed by 1 week without a patch to allow withdrawal bleeding. The overall annual probability of pregnancy is reported to be 0.8% and the method failure probability to be 0.6% [36]. As compared to OCs, compliance was observed to be better with the patch and high satisfaction was reported by the users [36–38].

2.3.2.2. Other transdermal methods in clinical development: Progestins with a high antiovulatory action at low doses could be used in transdermal systems as the total dose needed for efficacy remains small. Based on comparative efficacy of progestins on ovulation suppression, low doses of LNG, gestodene (GES), or NES would be active in transdermal systems [19]. These progestins are combined with an estrogen in most cases.

Selection of EE is most frequent estrogen in the new delivery systems as it can be used at a very low dose. However, due to its slow metabolism, EE whether delivered orally or via the transdermal route induces metabolic changes, it was shown that even when administered vaginally, EE increases liver proteins and coagulation factors and may increase the risk of VTE [39]. E2 is a much less potent estrogen than EE and its impact on liver proteins and coagulation factors is almost nil when administered transdermally [40]. E2 is metabolized more rapidly and extensively to inactive metabolites than EE, a difference attributed to the 17α-ethinyl group of the EE molecule [41]. In other studies conducted in postmenopausal women, it was shown that the risk of VTE is lower in users of transdermal E2 as compared with oral E2 [42]. Therefore, the selection of E2 rather than EE in a transdermal formulation appears attractive in order to improve the safety profile of hormonal contraceptives. However, this benefit would remain true if the progestin combined with E2 is a non-androgenic molecule. For progestins such as LNG and GES, EE is preferable to counteract the partial androgenicity of the molecules [43].

A new combined transdermal patch containing a total dose of 1.9 mg of gestodene and 0.9 mg of EE is under development. Given the high potency of gestodene, a very low daily dose can be administered. The dose of EE delivered at 9 mcg/d is lower than that of the currently approved patch. A pharmacodynamic study has shown that this combination suppressed ovulation in all 199 women in a study over two cycles [44].

Another patch which contains only the progestin LNG is in Phase II testing on ovulation suppression and follicle size [45]. This progestin-only patch would have the advantage of compliance over daily intake of low doses of LNG and would be appropriate for use in women with contraindications to estrogen or for women who are breastfeeding.

The same progestin LNG is also combined with EE in a 7-day patch and here also the androgenicity of LNG should be sufficient to counteract the action of EE on estrogen-dependent liver proteins such as SHBG (43). It was shown in the first pharmacokinetic study that the EE and LNG daily exposure during treatment with the combined patch was within the range reported for a low-dose COC [46].

The non-androgenic progestin NES has been tested in the form of a transdermal gel and was found to be highly effective in suppressing ovulation. A dose of 1.2 mg/d leading to an absorption of 120 mcg/d of the progestin was shown to suppress ovulation in 83% of the

study subjects in the first multicentric study [47]. Preliminary dose-finding results from a following study conducted with another formulation of a transdermal gel combining NES with E2 indicate high efficacy in suppression of follicle growth and full suppression of ovulation, with sufficient estrogen replacement with low doses of both steroids (Population Council, data on file).

Another transdermal contraceptive method, the Metered Dose Transdermal System (MDTS)is in its initial stages of development for delivery of NES and an estrogen,. A fast-drying liquid formulation is used in a non-occlusive spray and can deliver NES through the skin surface via a precisely engineered system. The serum levels of NES achieved with this system was found to be within the range of 285–290 pmol/L which is sufficient to block ovulation and hence would provide effective contraception [48]. A spray formulation incorporating both NES and an estrogen (EE or E2) is undergoing initial pharmacokinetic studies.

2.4. Future Development of Contraception “on-demand” for occasional use—

The use of LNG emergency contraception (EC) tablets, to postpone ovulation after an act of unprotected intercourse, is being tested for use before or after intercourse, by women who have occasional intercourse and do not need regular contraception.

Research on other molecules able to block the factors involved in the ovulation pathway is ongoing and in animal models of superovulation, ulipristal acetate UPA has been shown to prevent the LH peak up to 8 h prior to the endogenous surge [49] This mechanism of action may explain the efficacy of the molecule in EC and also opens the way to identify other molecules acting very late in the cascade of events leading to the LH surge.

Vaginal gels are being investigated for a possible role as a peri-coital ‘on-demand’ contraceptive agent which may be useful for women who have occasional intercourse and do not need a regular contraception. Levonorgestrel (LNG) in a dose of 750 mcg per 4 mL of Carraguard vaginal gel prevents or delays follicular rupture and induces ovulatory dysfunction in 96% of the cycles within 5 days of gel application [50]. Further studies are being conducted with other formulations to determine the duration of the effect on cervical mucus after gel administration and assessing the duration of application before intercourse to be fully effective. Future developments also include the combination of the contraceptive to an antiretroviral agent for dual contraception and protection against sexual infections transmissions before intercourse or on demand.

2.5. Long-acting reversible contraceptives (LARC)

2.5.1. Intrauterine contraception (IUC), devices (IUDs) and systems (IUS)—

The initial attempt to use an IUD dates back to about 100 years ago when an inert device in the form of the Graefenberg ring was used. Medicated devices containing copper or progestin were introduced half a century later. The research work from the Population Council and the ICCR has been instrumental in developing the Copper T200, Copper T380A and the LNG-IUS that have been used by millions of women over the world [51]. Today, the intrauterine system (IUS) that releases LNG at a slow steady rate of 20 mcg/day is widely used and has demonstrated high contraceptive efficacy for a duration of 5 years [52]. The LNG-IUS is currently marketed as Mirena® (Bayer Health Care) showing high efficacy and additional non-contraceptive benefits, especially for the treatment of heavy bleeding [53].

2.5.1.1. Systems in clinical development: Other progestins or PRMs have been tested in new IUSs with the common objective of creating an atrophy of the endometrium, and decreasing bleeding to even less than what is observed with the currently approved LNG-IUS [54].

Two low-dose levonorgestrel IUSs (12 and 16 mcg per day) that are smaller than the current 20 mcg system are in clinical development. The Phase II results indicated that lower doses of LNG12 mcg/d and 16 mcg/d (LNG-IUS12 and LNG-IUS16) provided effective contraception for 3 years, acceptable bleeding patterns, and were well tolerated compared with Mirena [55] A Phase III trial of another levonorgestrel-releasing intrauterine system (20 mcg /day) similar in design to Mirena® has been recently completed [56].

Also, safety and acceptability of three different doses of etonogestrel-releasing medicated intrauterine systems (ENG-MIUS) have been tested and this new system may become available in the near future [57].

The concept of using an IUS to deliver low doses of a PRM has been proposed with the objective of inducing complete endometrial atrophy and amenorrhea. An IUS releasing ulipristal acetate (UPA) has been found to be effective in the suppression of endometrial growth in primates [58] and extrapolation of these results to the human endometrium needs to be established. Because dose and species heavily influence the effects of PRMs on the endometrium, it is possible that UPA may act differently on the endometrium if delivered in low doses by IUS directly in the uterine cavity.

The use of a well tolerated PRM may be another good option provided that the targeted atrophic effect on the endometrium is obtained. Brenner et al. [59] showed that the androgen receptor (AR) overexpression was a functional component of the mechanism through which progesterone antagonists (PAs) induce endometrial anti-proliferative effects in the presence of estrogens. Therefore, a decrease in endometrial thickness and bleeding is expected with the local delivery of a PRM or a PA [60].

Bayer PA molecules which include ZK137316, ZK 230211 have also been tested in animal models for possible delivery from an IUS [61]. Subsequently, a short 4 to 8 weeks pilot study conducted in 42 women compared the IUS delivering the PA and the LNG-IUS. Short-term intrauterine release of ZK230211 did not change bleeding patterns or result in endometrial suppression. However, days of bleeding and spotting were unchanged by the use of ZK-IUSs but were increased by LNG-IUS ($P < 0.01$). Expression of proliferation markers was low following the use of both IUSs [62]. Further development of such systems may bring about a new long-acting method with better bleeding patterns. Long-term studies are warranted to demonstrate efficacy and safety.

2.5.2. Subdermal implants—The first sub dermal implant developed by the ICCR at the Population Council and known as Norplant® consists of six capsules 3 cm long containing LNG in a silicone elastomer matrix releasing LNG at a rate of about 40 to 50 mcg/day, and active for 7 years. A subsequent implant known as Jadelle®, also developed by the ICCR and the Population Council, was designed as an improvement over Norplant, in that it contained only two rods 4 cm long containing LNG with the same release rate as that of the six-capsules of Norplant, and is was active for 5 years. Although Norplant is no longer available in the United States due to litigation issues associated with difficulties in removal by untrained health personnel, it continues to be used by millions of women in developing countries worldwide and will be progressively replaced by the 2-rod Jadelle. A postmarketing surveillance of Norplant carried out in eight developing countries demonstrates a high contraceptive efficacy and low incidence rates of reproductive health problems [63]. Jadelle is also currently not marketed in the United States, although it received FDA approval in 1996, but is available in other countries. However, due to cost issues, several organizations developed a generic form of Jadelle, known as Sino-implant, manufactured in China.

A recently developed contraceptive implant, Implanon®, approved in the USA and worldwide, consists of a single rod implant delivering the progestin etonogestrel (ENG) with an initial release rate of 60 mcg/day. Its contraceptive efficacy is reported to be above 99% over three years of use [64].

2.5.2.1. Agents in clinical development: 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 lack of funding. A study on the clinical performance of NES implant in 100 breastfeeding women reported no pregnancy [65], The advantage of Nestorone implants in the postpartum period would be high as the progestin 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 and no serious adverse events were observed in the long-term study comparing the NES implant to the T-Cu IUD [65]. Lactational amenorrhea was significantly longer in NES users (353 ± 20 days) than in T-Cu users (201 ± 11 days).[65] When used in non-lactating women, this method seemed less effective with a 2-year cumulative pregnancy rate of 1.7 per 100 and dose-adjustment would be required for full efficacy over 2 years or longer [66].

Nomegestrol acetate subdermal contraceptive implants have also been advocated for further development as a multicenter one-year study showed these implants to be effective and well tolerated, with a 12-month net cumulative pregnancy rate of 0.94% [67].

3.5.3 Injectables—The available progestin-only injectables included in the current methods of contraception are norethisterone enanthate (NET-EN) and DMPA (depot medroxyprogesterone acetate) or Depo-Provera® which has been approved by the FDA since 1992 and is the most commonly used injectable in the United States. Lunelle® or Cyclofem, a combined injectable which consists of 25 mg MPA and 5 mg estradiol cypionate is no longer available in the United States but is widely used in Latin America and some parts of Asia. Injectable contraceptives of DMPA (without estrogen) have been associated with a potential lowering in bone mineral density when used at the time of peak bone mass building in young women [68]. Concern about bone loss, especially in adolescents, led to recommendations that DMPA be used in a lower dose form and for only 2 years in young women, although there have been no reports of increased fracture incidence in DMPA users [68].

A Cochrane review comparing DMPA (150mg every 3 months) and NET-EN (200mg every 2 months) injectables show no difference in efficacy but more frequent amenorrhea in DMPA users [69]

Other injectables using progestins better tolerated than DMPA and possibly with a longer duration of action are being researched as they may improve the use of this method found convenient by many women, especially in sub-Saharan Africa.

In addition, development of a self-injectable system, Uniject®, may considerably improve the method if it becomes a user-controlled self-injectable and require less trained providers.

3. Safety profile of hormonal contraceptives

The recent controversy about the possible increase in thrombosis risk in women using combinations of EE and a new anti-androgenic progestin is still ongoing [20, 70, 71].

Different studies led to different results showing either no difference in risk as compared to second generation pills containing levonorgestrel (active surveillance prospective studies) or

an increase in risk (observational or database studies). Several risk factors have to be taken into consideration and, in particular, obesity, sedentarity life style, and smoking and these factors were not adjusted for, in some of the observational studies [20, 71]

Hormonal contraceptives affect a variety of metabolic factors including hemostatic variables. lipid profile and carbohydrate metabolism. As OCs have been shown to induce rare cardiovascular events mainly venous thromboembolism (VTE) [20, 70, 71], several approaches have been implemented to improve the safety of hormonal contraceptives such as lowering the estrogen dose, modifying the estrogen type, selecting newer progestins, new administration schedules and alternative routes of delivery.

The estrogen component in the form of EE modifies some estrogen-sensitive hemostatic factors and liver proteins and these effects can be modulated depending upon the type of progestin [19]. Whether given by the oral route or vaginal route, the action of EE is found to remain the same [39]. The pronounced hepatic effects of oral EE are attributable to its chemical composition, specifically its 17alpha-ethinyl group which results in a slow metabolism and long tissue retention, rather than to the first-pass effect through the liver [41, 72]. This effect would not be observed with E2 and E2V as they are rapidly metabolized to estrone by the 17β-hydroxysteroid dehydrogenase. However, long-term studies of arterial and venous risk in users of the novel combinations associating non androgenic progestins and E2 or E2V are still ongoing and the likely improved safety profile cannot be determined until demonstrated in large outcome studies.

4. Methods with dual benefits

The noncontraceptive health benefits of contraceptives is an emerging area of interest. Use of hormonal contraceptives has improved women's lives by reducing different health conditions that contribute to considerable morbidity.

COCs are effective in significantly reducing blood loss in women with heavy menstrual bleeding [73]. Oral E2V and dienogest were found to be highly effective in the treatment of women with heavy menstrual bleeding (HMB) and this combination has recently been FDA-approved for that indication [74]. Similarly, the LNG-IUS has been shown to be as effective as endometrial ablation/resection in the management of HMB [75].

COCs and the LNG-IUS are effective in reducing *dysmenorrhea* [76]. and HMB [77] with a decrease in lost days of work [78]. Also, some combined OCs are also being used in the treatment of *acne* and *premenstrual dysphoric disorder* [79–80].

In addition, longer term benefits have been shown. Use of COCs' is associated with around 25% *reduction in fracture risk* among women in their 40s [81], as well as p*revention of tumors* such as benign ovarian tumors [82], and a decreased risk in ovarian, endometrial and colorectal cancers [83].

Research and development of new methods that would bring additional health benefits may improve willingness to use the method and increase compliance. As new areas of research, the potential of PRMs to prevent breast cell proliferation as previously shown by our lab and others [84], or the neuroprotective effects of progesterone and similar molecules such as Nestorone [85, 86] are highly medically relevant, supporting the research and development of such contraceptive molecules.

4.1. MultiPurpose technologies (MTP)

There is an urgent need, especially in less developed countries, to help women protect themselves against sexually transmitted infections, in particular HIV/AIDS, and to prevent unwanted or mistimed pregnancies. Several organizations are currently developing *dual protection vaginal rings* that deliver both LNG, a well-known contraceptive steroid, and an antiretroviral agent (ARV), including tenofovir (developed by CONRAD), Dapivirine [developed by the International Partnership for Microbicides (IPM)] or MIV-150 (developed by the Population Council).

A combination of an ARV and LNG as a single product for dual purpose, and in a user-controlled method that does not require trained providers to insert and remove, such as a monthly or 3-monthly vaginal ring, could potentially fill an important prevention gap as a multipurpose technology (MTP), a concept developed by the US Agency for International Development (USAID) for dual protection against HIV transmission and unwanted pregnancies.

Barrier methods offer the added advantage of protection against sexually transmitted infections including HIV/AIDS. The role of *spermicidal microbicides* in prevention of pregnancy has been tested and a low pregnancy rate per 100 women has been observed with Buffer gel (10.1%) and with nonoxynol-9 (12.12.3%) [87]. Cellulose sulphate gel is also seen to yield a six month pregnancy rate of 3.9 % with perfect use and 13.4% with typical use; which is comparable to the pregnancy rate seen with nonoxynol-9 [88], Similarly, the 12 month pregnancy rate with the spermicide C31G reached 13.8% compared to a rate of 19.8% with nonoxynol-9 [89]. The latter agent may soon be phased out as it was shown to increase the risk of HIV infection possibly as a result of damage to the lower genital tract epithelial surfaces [90]. *Vaginal gels delivering an antiretroviral* (ARV) agent-only such as Tenofovir (TFV) Gel developed by CONRAD or a combination of ARV (MIV-150) associated with zinc and a contraceptive progestin LNG(MIV-150/Zn/LNG) in a Carrageenan gel developed by the Population Council for dual purpose are promising methods to prevent STD and especially HIV transmission in combination with a contraceptive method. The *SILCS diaphragm* which is a single size silicone contraceptive device, when used with nonoxynol gel, reduced the average number of progressively motile sperm per high power field in the cervical mucus from a baseline of 12.5 to 0 [91]. A *new female condom* which is thin and soft and can easily be inserted like a tampon has been developed by the Program for Appropriate Technology in Health (PATH) and is presently undergoing Phase III clinical trials.

The latter devices are also combined with active agents. The SILCS Contraceptive Barrier is being combined with TFV gel and the woman's condom with a microbicide film.

5. Non-hormonal agents for female contraception

Cyclooxygenase-2 (COX-2) inhibitors such as Meloxicam administered orally in a dose of 30 mg for five consecutive days in the late follicular phase suppresses follicular rupture and may provide an alternate source of emergency contraception [92]. Use of another COX-2 inhibitor, rofecoxib, has also demonstrated delayed follicle rupture, more than 48 h after the LH peak [93]. Further studies assessing the safety of these molecules are needed.

Non-hormonal approaches in women target meiosis as well as genes involved in follicular rupture and ovulation. Research has been targeted to phosphodiesterase (PDE3) inhibitors that impair oocyte maturation [94] or to genes involved in the meiosis as an oocyte-specific meiosis inhibitor [95]. Also, research has been directed to inhibition of cumulus-oocyte complex expansion and inhibition of follicle rupture [96]. Prostaglandins such as PGE2

induce expansion of the complex. Antagonist molecules to the PGE2-Receptor may block this event. Another approach relates to the action of matrix metalloprotease (MMP) inhibitors on follicle rupture. In cultured follicles from primate monkeys, LH-induced mitogen-activated protein kinase (MAPK) activation is partially inhibited by an inhibitor of MMP shown to block follicle rupture, and maintained luteinized follicle unruptured with secretion of P levels [97].

In female mice, mutation of an antigen known as zygote arrest (ZAR1) has resulted in infertility [98]. Other targets include molecules which transform the endometrium in the preimplantation period under the dependence of P, including leukemic inhibitory factor (LIF), calcitonin, vitronectin, and integrins [99]. Inhibitors of these molecules could serve as potential contraceptive agents.

6. II Male contraception

6.1. Hormonal methods (see manuscript E. Nieschlag in this issue of the Journal)

As far as methods for men are concerned, simplicity, reversibility, and effectiveness are the desired features for a male contraceptive.

Male hormonal contraception include treatment with androgen alone or in combination with progestin or feedback suppression of pituitary gonadotropin (FSH and LH) with an analog of the gonadotrophin releasing hormone (GnRH) which results in reduction of sperm output [100, 101]. Clinical trials are focused on combinations of testosterone with a progestin such as MPA, LNG, desogestrel or norethisterone. No combination has achieved 95% azoospermia so far.

Potential adverse effects on prostate gland growth, when high doses of androgen are used, may be circumvented, with the development of tissue selective or androgen receptor modulators (SARMs) that could theoretically suppress gonadotropin secretion more profoundly, but possess reduced side effects on the prostate, due to lack of interaction with the 5α-reductase enzyme.

The Population Council has identified a synthetic androgen, 7α-methyl-19-nortestosterone (MENT), that is resistant to 5α reduction in the prostate and is also 10 fold more potent than T in terms of its anabolic effects and gonadotropin suppression with less prostate-stimulating activity than T [102]. This makes it an ideal androgen for exogenous administration for contraceptive and/or replacement purposes with health benefits

However, one of the barriers to universal application of male hormonal contraception is its delayed onset of action. Combination with a potent antigonadotropic agent that will suppress LH and FSH quickly during an initiation phase and ensure maintenance of such effect with MENT would be a successful option that should be tested in clinical trials. Another approach is to provide steady state delivery of both T and a progestin while avoiding high peaks and low troughs observed with oral pills and injectables and to develop a user-friendly male hormonal contraceptive method, Ilani N et al. [103] evaluated the efficacy of transdermal delivery of both steroid hormones in suppressing spermatogenesis in a 6-month study and showed a high rate of efficacy on sperm suppression. The authors combined T gel with placebo or Nestorone (NES, 16-methylen-17α-acetoxy-19-norpregn-4-ene-3, 20-dione) gel applied daily on the skin. An earlier pilot study using NES gel combined with T gel in healthy men for 20 days resulted in effective suppression of gonadotropins [104], prompting the 6-month study to evaluate this gel-gel combination as a provider independent long-term male hormonal contraceptive regimen.

The addition of NES to T resulted in significantly lower sperm concentrations and serum gonadotropin levels compared with T gel alone, but did not add additional side effects, which were minimal in all groups. Mean serum total and free T concentrations were maintained within the normal range throughout the treatment period in all groups. Therefore, this new method looks promising and further studies are warranted

Most of the studies using androgen and progestins were conducted in small groups of volunteers and large studies testing either a combination of etonogestrel implants and testosterone undecanoate injections [105] or the WHO large efficacy study testing norethisterone enanthate combined with testosterone injections have both shown high efficacy on sperm suppression. However, the former was the result of a collaboration between two pharmaceutical industries that have withdrawn from this field of research, and the WHO study was interrupted due to a high number of side effects, most likely the result of high dose combinations of both hormones [106].

Therefore it seems that new type of molecules should be designed and combinations with newer progestins with SARMs may be a better avenue for future development.

6.2. Non hormonal methods (see chapter from John Amory in the same issue of the journal)

Research on specific targets of the reproductive system should produce less side effects with more specific targets than with hormonal contraceptives. While clinical research on hormonal methods is advanced, non-hormonal methods are still at an early stage of research. New areas of basic research include studies on genes, proteins and enzymes involved in the reproductive system. New approaches target maturation of germ cells, a critical component of sperm development, or sperm motility and maturation in men. One approach includes disruption of the tight junction between sertoli cells, by analogs of Lonidamine, such as Adjudin [Aherens Junction Disruption] which inhibits movement of the germ cells, resulting in release of immature sperm [107].

These methods both for men and women aim at inducing reversible infertility without interfering with hormones secreted by the hypothalamus, pituitary gland, and the testis or ovaries, targeting specific interactions within the reproductive system at the level of the ovaries and testes, as well as between spermatozoa and ova.

This futuristic approach still keeps in mind the need for better access to existing contraceptive methods, as well as the discovery of new delivery systems that can deliver the new molecules directly to their specific targets, and methods that are simple to use, safe, reversible and inexpensive, a major challenge for the next decade.

7. Emerging science and future of contraception. Conclusion

Development of novel contraceptives which are effective and safe is on the horizon with a better understanding of reproductive biology.

Since the 2004 Institute of Medicine report, where recommendations were made for initiating discussions with the pharmaceutical industry about the development of new and innovative contraceptive targets, based on the rapid expansion of new technologies, and the genomic and proteomic revolution (the “omics”), the pharmaceutical industry has jettisoned many contraception R&D programs. Prospects of innovative contraceptives for females and males (both hormonal and non-hormonal) have suffered a serious setback. The working group on contraception in the Scientific Vision Workshop on Reproduction convened by the National Institute of Child Health and Human Development (NICHD) recognized that the

NICHD would now need to take the lead in contraceptive R&D and change the research paradigm in this field [2].

Ideally research objectives in the field of contraception include the improvement of existing methods, their proper use with increased access to the users, and the development of new methods which would bring additional health benefits with the goal of improving willingness to use the method and compliance.

Improvement of existing contraceptive methods includes working to improve their safety and acceptability; improving cycle control in users of hormonal contraception; developing approaches to improve adherence, convenience and access to contraceptives; developing ways to increase the use of long-acting, reversible contraceptives; understanding what non-contraceptive health benefits of contraceptives are valued by users, more effectively communicating those benefits, and developing additional benefits based on end-user desire; developing programs to increase successful contraceptive use in order to achieve actual efficacy. These strategies will ensure the most effective use of current contraceptive methods, while new contraceptives are developed [2].

New contraceptive development would include better mid-acting and long-acting reversible contraceptives (LARC); methods that will be user-controlled and easy to distribute; better methods for spacing births that can be used by breastfeeding women; on-demand methods for women who have occasional intercourse and do not need a regular method; methods for men that would be reversible, in contrast to vasectomy, and not related to intercourse such as condoms. New tissue-selective androgens, without action on the prostate, delivered from a one-year implant, are being developed. Non-hormonal methods are less advanced but new promising targets specific to the male reproductive system have been identified and are still in preclinical research.

We need to recognize that the fields of infertility and fertility intersect and should be collectively mined for contraceptive research and development. Also, we should identify these molecular controls of gametogenesis and fertility that can then be applied to contraception. Finally we need to develop innovative strategies to identify selective and druggable targets that will lead to new contraceptive modalities with fewer side effects and with non-contraceptive health benefits (2).

Remarkable progress in the field of genomics and proteomics has led to the development of animal models such as a transgenic mouse model, with a better understanding of the complex process of reproduction. Further, behavioral assessments/indicators that predict acceptability/successful use of new contraceptives should also be developed.

The contraceptive efficacy of the new long-acting methods is the highest developmental priority among contraceptives as these methods do not rely on daily compliance. While implants and IUD/IUS require a health provider for proper insertion and removal, vaginal rings and transdermal patches or gels have the advantage 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. The range of contraceptive options for breastfeeding women needs to be widened. In addition, today‘s research on new contraceptives, targets not only the prevention of unwanted pregnancies, but also additional 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 HIV 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.

Successful accomplishment of these research objectives will increase the safety, efficacy and use of existing contraceptives, expand acceptability of, and access to, contraceptives by the introduction of new methods, and move toward the goal of eliminating unintended pregnancies and improve maternal and child health on a global scale.

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