REVIEW ARTICLE

Pharmacology research exploring contraception

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AIM: The aim of this research article is to explore those areas where pharmacology research can contribute new insights concerning contraceptive possibilities.
METHODS: The method consists in an in-depth analysis of available publications on birth control and family planning emanating from the most influential sources and a comparison of conclusive versus inconclusive data found in these publications.
RESULTS AND CONCLUSION: The result is evidence for flawed data in presently available publications. The conclusion stipulates continued pharmacology research not only on mechanism of action, adverse events, and interactions but also on the parameter of safety.
Key Words: *Drug interaction; Contraception; Family planning; Birth control*
Abbreviations: LARC: Long Acting Reversible Contraception; EC: Emergency Contraception; OCs: Oral Contraceptives; EE: Ethinyl Estradiol; LH: Luteinizing Hormone; FSH: Follicle Stimulating Hormone; GnRH: Gonadotropin Releasing Hormone; EH: Endometrial Hyperplasia; OCSs: Oral Contraceptive Steroids; BMD: Bone Mineral Density; IUDs: Intrauterine Devices; FDA: Food and Drug Administration; WHO: World Health Organization.

INTRODUCTION

Presently, contraception appears to be the most frequently implemented strategy of family planning and birth control in most countries of the world. Originally only a gynecological issue, it has evolved during the last decades into a multi-billion business world-wide thriving on the sale of pills and devices. This economic success is due to ongoing pharmacological research that has supplied the world market with relatively safe and effective products. This research, however, has not yet reached a final stage but continues to strive for products that are increasingly safe and effective.

The following discussion aims at providing an impetus for this research by exploring the most pertinent parameters in contraception, namely efficacy and safety. In pursuing this aim the most salient areas are highlighted such as mechanism of action, adverse events, and interactions.

DISCUSSION

Despite long-standing pharmacological and medical research, not all aspects of contraception are fully understood and some areas need particular attention in future investigations as they are the basis for personalized medicine. These areas must be seen from the perspective of the clinical practice where contraceptives can be divided into four categories:

Oral hormonal contraceptives as the most widely used,

Long Acting Reversible Contraception (LARC) as the most effective,

Non-hormonal methods as the safest, i.e., causing no harm, and

Emergency Contraception (EC) as an ultima ratio to prevent pregnancy.

Oral hormonal contraception – the most widely used form of contraception

Common English language use considers contraceptive as an agent which prevents contraception, such as a medicated jelly in the vagina, a condom, a cervical pessary or diaphragm, or a systemically acting steroid that inhibits ovulation [1]. According to German researchers, a distinction has to be made among ovulation inhibitors (Oral Contraceptives (OCs) and parenteral depot gestagens), contraceptives which do not affect ovulation e.g., the minipill and interceptives which prevent implantation e.g., morning after pill [2]. As oral hormonal contraceptive methods German gynecologists described in the year 2000 combined pills Kombinationspräparate i.e., 1-Phasenpräparat), modified combined pills Mehr-Stufenpräparate, sequential (2-Phasenpräparate), and the Minipille a low-dose gestagen-only pill containing gestagens such as levonorgestrel, lynestrenol, and norethisteron. The Mikropille contains less than 50 µg of Ethinyl Estradiol (EE). For purposes of comparison, the first pill on the market was a combined pill, i.e., Enovid, containing 9.85 mg norethynodrel and 0.15 mg mestranol [2]. The first micropill was introduced as Microgynon in 1975 and contained 0.15 mg levonorgestrel and 30 µg EE [2].

Summaries of OCs are nowadays easily available also in social media [3]. Such summaries explain that the classic form of the pill after Pincus is a combination of estrogen, primarily EE and gestagen. The micropill as a low-hormone pill contains less than 50 mcg/d estrogen and about 150 mcg/d gestagen. The micropill is again subdivided according to the variation of the concentration of the hormone, namely one-phase pill (concentration constant during the entire cycle) and sequential pill (estrogen only during the first phase and gestagen only during the second pase), with the advantage of fewer cycle irregularities than in the one-phase preparation. The step-up-pill (Zweistufenpille) is similar to the Zweiphasenpille, but contains already during the first phase a small amont of gestagen. The Dreistufenpille contains variable estrogen and gestagen doses in three phases according to the level of hormones during the normal menstrual cycle [3].

Scholarly discussions of OCs add only details to the popularizing publications, but state basically the same facts as can be seen from a publication of 2013 in a widely used medical reference book [4]. In this publication the administration of a placebo is emphasized for combination OCs: For most combination OCs, an active pill (estrogen plus progestin) is taken daily for 21 to 24 days. Then, an inactive (placebo) pill is taken daily for 4 to 7 days to allow for withdrawal bleeding. In some products, the placebo pill contains iron and folate (folic acid); in others, this pill is not truly inactive but contains 10 mcg of EE [4]. This study addresses also the question of dose and explains that most combination OCs contain 10 to 35 mcg of EE. This dose is considered low, and low-dose OCs are usually

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preferred to high-dose OCs (50 mcg of estrogen) because low-dose OCs appear equally effective and have fewer adverse effects, except for a higher incidence of irregular vaginal bleeding during the first few months of use. One new product uses estradiol valerate instead of EE [4]. This study also addresses efficacy and considers all OCs as having equal efficacy i.e., the pregnancy rate after 1 yr is 0.3% with perfect use and about 9% with typical (i.e., inconsistent) use [4].

Mechanism of action: Not all of the above mentioned studies offer a discussion of mechanism of action, which is a central topic in physiology research. As early as 1995 the physiological changes have been described and explanations have been provided for the effects of estrogens and progestin [5]. In a summarizing fashion it has been stated that women who undergo long-term treatment with relatively large doses of estrogen do not ovulate, probably due to depressed Follicle Stimulating Hormone (FSH) levels and multiple irregular bursts of Luteinizing Hormone (LH) secretion instead of a single mid-cycle peak. When women are treated with similar doses of estrogen plus a progestational agent, they do not ovulate because the secretion of both gonadotropins is suppressed. Moreover, progestin makes the mucus thick and improper for sperm migration, interfering probably also with implantation. For the purpose of oral hormonal contraception, an orally active estrogen such as EE is combined frequently with a synthetic progestin such as norethindrone. The pills are administered for 21 days, then withdrawn for 5-7 days to allow menstrual flow, thereafter started again [5]. Norethindrone, similar to EE has an ethinyl group on position 17 of the steroid nucleus, and as a consequence it is resistant to hepatic metabolization. Although it is a progestin, it is partly metabolized to EE and has therefore also estrogenic activity. It is now clear that small as well as large doses of estrogens are effective. The use of small dose reduces the risk of thromboses or other complications. Progestins alone can be used for contraception, although they are more effective when combined with estrogens [5]. This claim of a higher efficacy of a combination of progestin and estrogen cannot be supported by contemporary research, such as research on contraceptive technology [6]. Contraceptive Technology presented a table in the year 2011, entitled CT Failure Table, consisting of a list of all available methods and percentages of women experiencing an unintended pregnancy during the first year of typical use and the first year of perfect use. In this table combined pill and progestin-only pill are listed with the same estimates i.e., 9% for typical use and 0.3% for perfect use.

In the year 2000 a description of physiological processes was presented by German gynecological research [2]. This research explained in similar terms the mechanism of action of OCs specifying that ovulation inhibitors block secretion of gonadotropins by the pituitary and have an effect also on hypothalamic secretion of Gonadotropin Releasing Hormone (GnRH) and Gonadotropin-Inhibiting (GIH) Hormone. Reduced secretion of FSH prevents maturation of the follicles, and due to the absence of a peak of LH, no induction of ovulation occurs [2].

Gestagens were described as increasing the viscosity of cervical mucus and preventing ascension of the sperms through the cervical canal. Moreover, the mid-cycle opening of the canal fails to occur. Due to progestagens, capacitation of the sperms is inhibited so that the acrosomal reaction, a pre-condition for the fusion of oocyte and sperm, does not take place [2].

Acrosomal reaction was understood as a breakdown of the lysosome-like organelle on the head of the sperm through which various enzymes are released, including the trypsin-like protease acrosin. Acrosin facilitates the penetration of the sperm through the zona pellucida. When one sperm reaches the membrane of the ovum, it fuses to the membrane. It appears that the fusion is mediated by a protein on the surface of the sperm head that resembles the viral fusion proteins which permit viruses to attack cells [5]. This description of the process of capacitation is still awaiting rectification through new studies, especially in view of modified assumptions on the role of the oocyte subsequent to the process of fusion.

What is important to note with regard to ovulation inhibitors is the claim that supply of progestagens during the proliferative phase of the menstrual cycle leads to a reduced formation of the endometrium and insufficient transformation during the secretory phase [2]. Such changes in the cervical mucus inhibit the nidation of the blastocyst. Moreover, it has been stated that the consistency of the tubal secretion and the tubal motility is altered by ovulation inhibitors, which also reduce the number and size of cilia. It must be remembered in this context that under physiologically normal circumstances the developing embryo i.e., the blastocyst moves down the tube into the uterus within 3 days during which the blastocyst reaches the 8-cell or 16-cell stage. Once in contact with the endometrium, the blastocyst becomes surrounded by an outer layer of syncytiotrophoblast and an inner layer of cytotrophoblast. The syncytiotrophoblast erodes the endometrium, and the blastocyst burrows into it (implantation) [5].

Estrogen component in oral hormonal contraception: The synthetic estrogens used in contraception are derived from the naturally occurring estradiol [2]. The most frequently used steroid is EE. Binding of EE to the estrogen receptor exceeds the binding of physiologic estrogens. Due to the ethinyl group on C-17, hepatic metabolization is delayed, and the substance remains longer active with a half-life of 7 hours [2].

Complete resorption of EE takes place in the proximal sections of the small intestine, and its qualitative effects are not different from the naturally occurring estradiol. Among these effects are stimulation of estrogen dependent tissue such as endometrium, myometrium, vaginal mucus, mammary gland, and urothel [2]. Concerning synthetic estrogen it has been observed that it is relatively active when given by mouth because it is resistant to hepatic metabolism. This is not true for naturally occurring hormones when they are administered by mouth because venous drainage of the intestine carries them to the liver, where they are inactivated before reaching the general circulation. Some nonsteroidal substances and a few compounds found in plants have estrogenic activity. The plant estrogens are rarely a problem in human nutrition, but they may cause undesirable effects in farm animals [5]. The synthetic estrogen diethystilbestrol and several related compounds are estrogenic, possibly because in the body they are converted to a steroid-like ring structure.

According to physiological research of 1995, estrogens have multiple effects especially on the female genitalia, endocrine organs, behavior, breasts, female secondary characteristics, salt and water retention, sebaceous glands, and plasma cholesterol [5]. On female genitalia, they facilitate the growth of the ovarian follicle and increase the motility of the uterine tubes. One of the most important behavioral effects is increase of libido in humans. In the breasts they produce duct growth and breast enlargement at puberty in girls. Breast enlargement that occurs when estrogen-containing skin creams are applied locally is due primarily to systemic absorption of the estrogen, although a slight local effect is also produced. Estrogens are responsible for the pigmentation of the areolas [5]. Concerning salt and water retention in addition to weight gain just before menstruation it has been underscored that aldosterone secretion is slightly elevated in the luteal phase, and this also contributes to the premenstrual fluid retention [5].

As early as 1995, there seemed to be sufficient evidence from a physiological standpoint that estrogen lowers plasma cholesterol, inhibits atherogenesis and avoids complications of atherosclerotic vascular disease in premenopausal women. Thus, small doses appear to reduce the incidence of cardiovascular disease after menopause. However, large doses of orally active estrogens promote thrombosis, apparently because they reach the liver in high concentrations in the portal blood and alter hepatic production of clotting factor [5].

As can be seen from this statement of 1995, one of the crucial problems with estrogen administration has been estrogen overdose. Currently information on overdose is available also in numerous public and social media where signs and symptoms are described in detail, namely breast tenderness, fluid retention, dramatic change in mood or temperament, drowsiness, headache, skin rashes, nausea, urine discoloration, vaginal bleeding that occurs in excess, a few days subsequent to the overdose incident [7].

To prevent the incidence of overdose, the standardized doses are specified in some publications, as for example in one from the year 2013, where the German journal of pharmacists commented on synthetic estrogens i.e., EE

and estradiol valerat [8]. For EE 15 µg, 20 µg, 30 µg, 35 µg and 50 µg are indicated. The low-dose pills containing 20 µg to 30 µg are recommended for two groups of women, namely younger women whose weight is below 50 kg and for women older than 35 years of age.

At that time, mestranol, the prodrug of EE was not available as combined pill. Regarding estradiolvalerat (the estherized form of the naturally occurring 17beta-Estradiol) whose 1 mg equals 0.76 mg estradiol, it was specified that it is fragmented during gastrointestinal resorption with the result that estradiol only remains effective undergoing a faster metabolisation than EE. In the case of a dose lower than 50 µg EE the designation Mikropille was considered appropriate. The amount of EE in most combined OCs was specified as ranging from 20 µg to 35 µg.

The dubiousness of standardizing dose has been brought to light in a publication emphasizing individual differences in the pharmacology of steroids. This study from the year 2010 draws attention to disposition and external factors, such as nutrition and medicines [9].

There are large individual differences in the pharmacology of contraceptive steroids, with both the disposition and external factors play a role (food, stimulants, drugs).

The importance of adjusting the dose of estrogens to the individual disposition has been emphasized also in a study of 2013 which draws attention to the need for higher doses in certain cases [10]. Although 20-30 mcg of EE are considered sufficient in this study for remedying estrogen deficit, this might not be true for younger women with restricted ovarian function due to anorexia nervosa or athletic activities. Suppression of ovarian function through combined pill is considered a risk for reaching peak-bone-mass. Normally, EE at a dose of 20-30 µg is sufficient to prevent estrogen deficiency. This may not apply to young women (<18 years) with limited ovarian function (e.g., competitive sports, Anorexia nervosa), as even low-dose combination drugs can suppress the ovaries and thus endanger the achievement of peak bone mass [10].

Besides estrogen overdose and standard dose important aspects of estrogen administration have been discussed in the literature, and the most noteworthy are presented in the following section in retrograde chronological order.

In 2012, a historical overview provided a summary of historical events related to oral contraception and an outlook on future developments [11].

In 2009, the risk of Endometrial Hyperplasia (EH) in relation to use of OCs as well as hormone therapy has been studied [12]. In their conclusion the authors state that previous findings of a causal relationship of estrogen-only hormone therapy and increased risk of EH deserves further investigation on users of oral contraception. This study suggests that previous findings of the association of estrogen-only hormone therapy with increased risk of EH and the lack of an association between estrogen plus progestin hormone therapy and EH risk are likely to apply to both complex EH and atypical EH. Further examination of the association between OCs and EH, with greater numbers of OC users, is warranted [12].

In 2003, the combination of Estrogen-Progestin oral contraception has been discussed in the context of a clinical case, where a 35-year-old healthy, sexually active woman presented for advice about the use of OCs. The discussion aimed at answering the question as to whether for such a patient an oral contraceptive should be prescribed, and if so, how a formulation could be chosen [13].

In the same year a genetics-oriented study investigated estrogen excess-aromatase gene [14]. This study is based on the assumption that aromatase is the key enzyme for estrogen biosynthesis. The aromatase gene (also referred to as CYP19) on chromosome 15q21.2 encodes aromatase messenger RNA (mRNA), which produces aromatase, an enzyme that converts C19 steroids to estrogens [14].

In 1991, Oral Contraceptive Steroids (OCSs) have been discussed as a pharmacological issue with a view to the clinical practice including advice for prescribing physicians [15]. The discussion assumed that OCSs are well absorbed from the gastrointestinal tract in humans. In contrast to progestogens which are almost completely bioavailable, EE2 is subject to extensive first pass metabolism consisting chiefly of conjugation with sulfate in the gut wall. Both EE2 and progestogens are well absorbed in patients with an ileostomy or with diseases such as cystic fibrosis or Crohn's disease. However in patients with celiac disease (gluten-sensitive enteropathy) the gut wall is less able to conjugate EE2 and thus its bioavailability is increased. Withdrawal of gluten leads to improvement and return to control values of the bioavailability. Among other drugs that are conjugated with sulfate are vitamin C and paracetamol. These compete for available sulfate when they are co-administered with OCs leading to high plasma levels of EE2. Enzyme-inducing agents such as rifampicin, phenobarbitone, phenytoin and carbamazepine reduce blood levels of the OCS leading to contraceptive failure [15]. Increased administration of OCs can prevent such a failure in the case of anti-convulsants but not in case of rifampicin. Concerning broad-spectrum antibiotics failure of contraception has been reported assumedly by interference with the enterohepatic circulation of EE2. Nevertheless practitioners are advised to recommend the use of alternative contraceptive precautions for women receiving broad-spectrum antibiotics concurrently with their OCS preparation [15].

As early as 1988, the inhibition of ovulation was studied by comparing the mechanism of action of steroids and GnRH analogues [16]. According to this study preliminary human data suggest that the administration of a GnRH antagonist during the follicular phase will inhibit ovulation. Unfortunately, the long-term administration of these compounds is contraindicated by their side-effect of a decrease in bone mass [16].

As early as 1980, the relationship between OCs and endometrial cancer in animals and women had been studied [17]. As one of their findings the authors state that no causal relationship between OCs and endometrial cancer can be established.

Cases of endometrial cancer have been observed in women using sequential OCs, particularly dimethisterone with EE, but a cause-and-effect relationship has not been established. Concerning protective effects, the authors state: “The progestin in combination OCs may offer some protection against endometrial neoplastic changes” [17].

As can be seen from the above cited studies, in several of them it is not only the effects of estrogen in premonopausal women but also postmenopausal hormone therapy that is addressed. One of the noteworthy studies investigated the topic of coronary heart disease, [18] where the authors conclude: Estrogen plus progestin does not confer cardiac protection and may increase the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use. This treatment should not be prescribed for the prevention of cardiovascular disease [18].

From a pharmacological perspective it seems imperative in this context to mention also the issue that is most closely related to contraception i.e., fertility. The issues of sterility and fertility have been addressed in numerous studies, and one from the year focused on aromatase inhibitors [19]. On the assumption that anovulation is likely responsible for 20% of female infertility, the authors agree with recent studies which found that aromatase inhibitors may be safe and useful agents for ovulation induction in patients with polycystic ovarian syndrome as well a treatment option for superovulation in patients with either unexplained infertility or endometriosis [19]. They conclude that aromatase inhibitors may be an effective alternative treatment to clomiphene citrate for both ovulation induction and superovulation [19].

Besides effects of estrogen, the injectable contraceptive depot medroxyprogesterone acetate has been investigated in numerous studies, especially its effect on Bone Mineral Density (BMD). Paradigmatic for other studies, a study of 2011 did not detect a deleterious effect [20]. In their conclusion the authors state: “Our study did not detect a deleterious effect on measurements of forearm BMD among long-term DMPA users with less than 13 years of use; however, a significantly lower BMD was observed at 13-15 years of use in DMPA users when compared to Intrauterine Devices (IUDs) users. BMD was inversely correlated to older age and directly correlated to Body Mass Index (BMI) (kg/m(2)) [20].

Interactions: As can be seen from the studies cited above, numerous topics have been investigated pertaining to steroids used in contraception and in some of them the topic of interactions has been addresses too, but not always in an exhaustive fashion. This topic of interactions, frequently neglected even in modern studies has a relatively long history because as early 2000, German researchers have systematically classified possible interactions in the form of a table, as can be seen from Table 1 [2].

Table 1: Oral hormonal contraceptives and possible interactions.

Interacting pharmacon	Mechanism of interaction	Effects
		Reduced absorption of steroids
	Bactericidal effect in intestine	Interruption of enterohepatic circulation
Antibiotics, Laxative	Increased intestinal passage	Contraceptive efficacy at risk
Benzodiazepin, Cumarin, Cyclosporin, Tricyclic antidepressant, Pethidin	Inhibition of cytochrom P 450 through oral contraceptives	Reduced oxidative metabolization oft interacting pharmakon (leading to slight increase of effect)
NSAIDs	Induction of hepatic enzymes through contraceptives	Accelerated elimination of analgesic leading to small reduction of effect

As can be seen from the above table, only a limited number of interactions of contraceptive agents are sufficiently known and continued research is needed to explore this wide area. This is true also for the most effective contraceptives, namely implants and IUD which are commonly designated as LARC. Intensified research on interactions might modify the frequently reiterated assertion that LARC can be safely used by almost all women.

Long- Acting Reversible Contraception (LARC)

The frequently encountered claim that LARC methods are the most effective [21] is based on statistical studies. Statistical data are provided by contraceptive technology which published as early as 2011 a systematic summary of all methods in the form of a contraceptive failure table (Table 2) [6]. According to this table a ranking of methods based on perfect use yields the following result.

Table 2: Ranking based on contraceptive technology (2011).

Method	Perfect/typical use
Implanon	0.05/0.05
Male sterilization	0.10/0.15
Mirena (LNg)	0.2/0.2
Depo-Provera	0.2/6
NuvaRing	0.3/9
Evra Patch	0.3/9
Combined Pill and Progestin-only	0.3/9
Symptothermal method	0.4/24
ParaGard (copper T)	0.6/0.8
Male condom	2/18
Ovulation method	3/24
Withdrawal	4/22
TwoDay method	4/24
Female condom	5/21
Standard Days method	5/24

Sub-dermal hormonal implants: According to one of the most recent studies on LARC from 2016 [21], Nexplanon was the only hormonal implant available in the U.S., as of 2016. This study described that Nexplanon slowly releases the progestin etonogestrel and differs from the previously marketed implant Implanon by virtue of an improved inserter and the presence of barium to facilitate the radiologic detection of implants that can no longer be palpated [21].

The contraceptive mechanism of action of the hormonal implant is considered as twofold: inhibition of ovulation and thickening of the cervical mucus. The contraceptive effectiveness of the implant is among the highest, with an estimated 0.1% of users becoming pregnant in the first year of use. BMI does not seem to have any influence on this estimate.

This etonogestrel-releasing implant is approved by the Food and Drug Administration (FDA) for 3 years of use. Proponents of implants have claimed that almost all women can safely use implants; exceptions are women who have hypersensitivity to barium or to the components of the implant [21].

However, it has been admitted that the use of the hormonal implant is considered to be contraindicated in women with current breast cancer and is generally not recommended in women who have had recent breast cancer. Unpredictable uterine bleeding and amenorrhea are considered as the most frequently encountered side effects, as has been stated as early as 1995 [5].

International agencies, as for example the British National Health Service underscore a larger number of adverse events, namely amenorrhea, change of periods, headaches, acne, nausea, breast tenderness, changes in mood, and loss of sex drive [22]. Research publications indicate precise data concerning side effects, namely 14.8% irregular bleeding, 16% headache, 12% weight gain, 12% acne, 10% breast tenderness, 6% emotional lability, 5% abdominal pain [23].

Intrauterine Devices (IUDs): According to the 2016 study on LARC [21], the FDA had approved five IUDs as of November 2016 which are available in the United States. The copper-containing IUD, ParaGard, is a non-hormonal device and contains 380 mm^2 of copper around the arms and stem.

Among the hormonal devices are four levonorgestrel-releasing IUDs (LNG-IUDs). Two of them, Mirena and Lilletta contain 52 mg of levonorgestrel. One device contains 19.5 mg (Kyleena), and a slightly smaller device contains 13.5 mg (Skyla). Liletta is marketed as a lower-cost option for clinics eligible for 340B pricing through the U.S. Department of Health and Human Services [21].

Regarding the mechanism of action of IUDs, it is claimed that IUDs do not cause the destruction of an implanted embryo but rather work primarily by preventing fertilization [21]. The copper-containing IUD releases copper ions that are toxic to sperm. The LNG-IUD inhibits ovulation and thickens cervical mucus, which prevents the penetration of sperm [21].

Concerning efficacy, it is claimed that less than 1% of women become pregnant during the first year of IUD use, with pregnancy rates with the LNG-IUD (0.1 to 0.2%) generally reported as lower than the rates with

the copper containing IUD (0.5 to 0.8%) [21]. These rates of 2016 correspond roughly with those indicated by contraceptive technology in 2011, namely 0.8% (typical use) and 0.6% (perfect use) for copper and 0.2% for levonorgestrel (both typical and perfect use) [6].

ParaGard is approved by the FDA for 10 years of use, Mirena and Kyleena for 5 years, and Skyla for 3 years. As of November 2016, Liletta is approved for 3 years of use, but data are being collected to assess 5-year use. Concerning continued use, a study project indicated that continuation rates with the LNG-IUD and the copper-containing IUD were 88% and 85%, respectively, at 1 year, 79% and 77% at 2 years, and 52% and 56% at 5 years [21].

Concerning adverse events and risks it has been stated as early as 1995 that the usefulness of IUDs is limited by their tendency to cause intrauterine infections [5]. Contemporary proponents claim that almost all women can safely use IUDs, [21] but a considerable number of exceptions have been listed such hypersensitivity to copper or hypersensitivity to other components of either type of IUD. In addition, the following medical conditions have been found to be irreconcilable with the use of an IUD: current pelvic infection or a Sexually Transmitted Disease (STD); gynecologic cancers; and certain other serious medical conditions, such as current purulent cervicitis or known chlamydial infection or gonococcal infection [21].

As can be seen from the studies on LARC, these methods do not require any adherence to a regimen as is the case with oral hormonal contraceptives where pills have to be taken on a regular basis. Despite this advantage, there are adverse events and risks, some of which might be serious enough to be considered as life-threatening, as for example perforation in the case of an intrauterine device. As a consequence, some women, especially those with reduced sexual activity, might be interested in only occasional contraceptive measures, as is made possible through EC.

Emergency Contraception – the ultimate opportunity to prevent conception

Presently, the literature on EC is abundant. This abundance is not surprising as it has been described quite accurately as early as 1999 [24]. One of the most recent publications that provide an extensive review of EC appeared in 2017 [25]. These reviews present two noteworthy findings, first the high efficacy of ulipristal acetate and second a rectification of the widely disseminated notion that EC should not be used as a regular form of contraception.

Ulipristal acetate has been discussed in numeros studies [26]. In the 2017 review the important claim is made that this medication is the most effective, although its estimates of effectiveness range from 62% to 85% which is lower than the least effective methods, such as chemical spermicides or coitus interruptus [2]. The antiprogestin ulipristal acetate (30 mg in a single dose) is the most effective ECP option in the United States and Europe, with reported estimates of effectiveness ranging from 62% to 85% [25].

Aside from this positive comment on ulipristal acetate, the other noteworthy claim pertains to the widely disseminated warning that EC should not be used as a regular form of contraception. This warning has been enunciated by such renowned organization as the FDA and the World Health Organization (WHO), so that the question arises on what grounds the 2017 review can rectify it. The rectification is the result of inquiries into the safety of current regimens in case of frequent use over a longer period of time. Despite a lack of data on the safety of frequent use of EC there is experience with similar regimens and with high dose OCs. This experience suggests that the likelihood of serious harm from at least moderate repeat use is low. Certainly, repeated use of ECPs is safer than pregnancy, in particular when the pregnancy is unintended and women do not have access to safe early abortion services [25].

Besides these two items, i.e., ulipristal acetate efficacy and safety of frequent use of EC, the review of 2017 does not provide any unexpected findings. For some women it might be interesting to know that assistance is available through the American Society for Emergency Contraception.

As is obvious, EC as a posteriori measure does not require compliance with a certain regimen for a longer period of time. The question of safety, however, is not yet resolved despite a statement reducing the dimension of safety to death or a serious medical complication. No deaths or serious complications have been causally linked to EC. According to the U.S. Medical Eligibility Criteria for Contraceptive Use (US MEC), there are no situations in which the risks of using combined, progestin-only or ulipristal acetate ECPs outweigh the benefits [25]. For some women the low efficacy of EC and the risk of a perforation through an IUD might in fact be serious enough to refrain from EC altogether.

If this is the case and traditional oral contraceptive methods are out of the question due to intolerance to hormones, women still have an option, namely natural non-hormonal contraception.

Fertility awareness (fertility awareness-based methods, natural family planning or periodic abstinence) – The safest form of contraception

As can be seen from an in-depth analysis of oral hormonal contraception, LARC and EC, adverse events, risks and complications can be serious. As a consequence, some women might be prepared to embark on birth control only under the condition that risks can be avoided. Avoidance is in fact possible because non-hormonal methods are readily available. Above all, the so-called Fertility Awareness-Based (FAB) methods receive increasingly attention, especially in Western Europe where the first investigations took place [2]. Van de Velde from the Netherlands described the Basal Body Temperature method as early as 1927. The Austrian Knaus together with the Japanese Ogino developed the Calendar or Rhythm method, and in 1964 the Australian John Billings delineated the Ovulation or Cervical Mucus method. The latter was then combined with the other methods as symptothermal method by the Austrian Rötzer. Extensive discussion of these methods and their assessments has been presented recently in a scholarly investigation [27].

Hitherto, these methods have not received particular attention in scholarly studies because their main benefit, namely safety in the sense of no harm, has been considered only marginally in ratings and rankings. In order to rectify this deficit, it seems appropriate to conceive of new ways of ranking contraceptive methods. The following table aims at accomplishing this goal. Besides safety, this ranking considers also convenience since this parameter is significant for the adherence to a certain method (see Table 3).

Table 3: Safety-efficacy-convenience ranking.

Method	Safety (No harm)	Efficacy perfect/ typical use	Convenience
Symptothermal	High	0.4/24	High
Ovulation	High	3/24	High
Two Day	High	4/24	High

Standard Days	High	5/24	High
Implant	Moderate (irregular bleedings)	0.05/0.05	High
Mirena (Lng) IUD	Low (Pelvic inflammatory disease=PID)	0.2/0.2	Low (Must be inserted by clinician)
ParaGuard IUD	Low (PID)	0.6/0.8	Low (Must be inserted by clinician)
Depo-Provera	Moderate	0.2/6	Moderate
Combined pill and Progestin-only Pill	Moderate (Thomboembolism in case of estrogen-containing pills, nausea, loss of libido, etc.)	0.3/9	Moderate (Pill must be taken everyday and at the same time. Prescription needed).
Evra Patch	Moderate	0.3/9	Low (New patch has to be used each week for three weeks (21 total days). No patch should be used during the fourth week. Prescription needed).
Nueva Ring	Moderate	0.3/9	Low (Ring can be placed by user herself into the vagina; ring should be kept in vagina for three weeks and removed for one week. Prescription needed.)
Male Condom	High	2/18	Moderate (Must be used at each coitus. Besides abstinence, latex condoms are the best protection against HIV/AIDS and other STIs).
Female condom	Moderate	5/21	Low
Diaphragm with Spermicide	Moderate	06/12	Low (Must be used for each coitus).
Emergency Contraception – If no method was implemented or efficacy of implemented method is uncertain. In some cases (decreased sexual activity) possible as a regular form of birth control			
Emergency Contraceptives, "Plan B, "Plan B One Step, "Ella, etc.	Moderate	7 out of 8 women would not get pregnant after using Emergency Contraceptives	High (Must be used use within 72-120 hours of unprotected coitus, is most effective when taken as soon as possible after the unprotected act. If used routinely because of merely sporadic sexual activity, clinician should be consulted.

Such a table which includes also safety and convenience might prove beneficial for women who are interested in finding a personally fitting method of contraception without consulting dozens of articles or websites. Equally, health care providers whose time is at a premium might prefer comprehensive tables to cumbersome research on reliable publications. Of course, the above presented table is not the first one to aim at providing succinctly the essentials of contraception. However, it is unique in its strife for completeness and accuracy incorporating also information contained in tables presented in the past.

Ratings and rankings of contraceptive methods

Among the numerous ratings and rankings of contraceptive methods, which can be traced back at least to 1982, [28] the most authoritative have been presented by highly influential organization such as the FDA, [29] the WHO, [30] the Centers for Disease Control (CDC), [31] the Office of Populations Affairs (OPA), and the American Congress of Obstetricians and Gynecologists (ACOG). The incongruities of these ratings and rankings have been rarely pointed out, but are also a topic of the study cited above [27].

As early as 1999 [24] a ranking according to preference has been presented claiming that oral hormonal contraceptives are the most preferred, followed by condom, coitus interruptus, periodic abstinence, gestagen injection, spermicidal agents, subdermal gestagen implants and intrauterin pessary. In addition to these most preferred methods sterilization is discussed by drawing attention to the advantages of vaginal hysterectomy. Albeit morbidity and blood loss are considered to be more substantial and hospital time longer than in tubal ligation sterilization, there are definitive advantages, i.e., efficacy is 100%, menstrual problems are eliminated, and the possibility of developing myomas or carcinomas of the uterus is annulled [24].

Currently, one of the most frequently consulted agencies is of course the FDA whose authority in matters of drugs and devices is frequently uncritically acknowledged. Thus, it is not surprising that a considerable number of women turn to the FDA in their quest for a fitting method of contraception. When doing so, they can find a survey of birth control methods which are approved by the FDA and listed in Table 4 [29].

Table 4: FDA Survey (2013) Food and Drug Administration (FDA) Approved Methods of Birth Control.

Methods	*Number of women out of 100 who will not get pregnant: perfect use	*With typical use, number of women out of 100 who will not get pregnant	How to Use It
Sterilization Surgery for Women	>99%	>99%	One-time procedure; nothing to do or remember.
Surgical Sterilization Implant for Women	>99%	>99%	One-time procedure; nothing to do or remember.
Sterilization Surgery for Men	>99%	>99%	One-time procedure; nothing to do or remember; condoms should be used for at least 3 months until stored sperm are cleared from the reproductive tract.

Implantable Rod**	>99%	>99%	Nothing to do or remember, lasts up to 3 years, inserted by clinician.
IUD**	>99%	>99%	Nothing to do or remember, lasts 3-10 years, inserted by clinician.
Shot/Injection	>99%	94%	Need a shot every 3 months, prescription needed.
Oral Contraceptives Combined pill: The Pill	>99%	91%	Must swallow pill every day, prescription needed.
Oral Contraceptives Progestin-only: The Pill	>99%	91%	Must swallow pill everyday. Must be taken at the same time each day. Prescription needed.
Oral Contraceptives Extended/ Continuous Use: The Pill	>99%	91%	Must swallow pill everyday. Prescription needed.
Patch	>99%	91%	Put on a new patch each week for three weeks (21 total days). Don't put on patch during the fourth week. Prescription needed.
Vaginal Contraceptive Ring	>99%	91%	Put the ring into the vagina yourself. Keep the ring in vagina for three weeks and remove for one week. Prescription needed.
Male Condom	98%	82%	Must use every time you have sex; requires partner's cooperation. Except for abstinence, latex condoms are the best protection against HIV/AIDS and other STIs.
Diaphragm with Spermicide	94%	88%	Must use every time you have sex.
Sponge with Spermicide	80-91%	76-88%	Must use every time you have sex.
Cervical Cap with Spermicide	74%	60%	Must use every time you have sex.
Female Condom	95%	79%	Must use every time you have sex. May give some protection against STIs.
Spermicide	82%	72%	Must use every time you have sex. Associated with risk of STI and HIV due to vaginal irritation with frequent use.
Emergency Contraception – If your primary method of birth control fails			
Emergency Contraceptives, "Plan B, "Plan B One Step, "Ella	85%	7 out of 8 women would not get pregnant after using Emergency Contraceptives	Must use within 72-120 hours of unprotected sex. It is most effective taken as soon as possible after the unprotected act. It should not be used as a regular form of birth control.

*Effectiveness rates are listed for "perfect use and "typical use.
**Implantable rod and IUD considered LARC and are highly recommended for young women who do not wish to become pregnant, but may want to have children later.
Source: Contraceptive Technology 20th, 2011.

Given the FDA's authority, most consumers will conclude that the survey is complete and includes all presently available methods. This conclusion, however, is fallacious because an in depth-analysis reveals serious shortcomings of this survey, in particular a substantial lack of information concerning the so-called fertility awareness methods.

In addition the FDA uses imprecise percentages indicating that certain methods accomplish remarkable perfect use estimates, but concealing that for certain methods the typical use estimates are inferior to their perfect use estimates. These discrepancies become patent in a comparison of the FDA survey with a table propounded by the WHO [30]. In the WHO table the distinction between perfect and typical use is redefined as Correct (and consistent) and common use [13]. A modified ranking according to WHO data can be seen in Table 5.

Table 5: Ranking based on WHO data (2017).

Method	Effectiveness: correct+consistent/common use	Disadvantages, adverse events and mechanism of action
Female sterilization (tubal ligation)	>99%	Surgical intervention
Implants	>99%	To be implanted by clinician. Irregular vaginal bleeding
Combined Oral Contraceptives (COCs) the pill	99/92%	Contains estrogen and progestogen.
Emergency Contraception (ulipristal acetate 30 mg or levonorgestrel 1.5 mg)	99%	Pills to be taken twice to prevent pregnancy up to 5 days after coitus.

Combined contraceptive patch and combined Contraceptive Vaginal Ring (CVR)	Allegedly comparable to COCs both correct (consistent) and common use	Prevents ovulation. Releases both estrogen and progestin. Pharmacokinetic profile comparable to COCs.
Progestogen-Only Pills (POPs) or the minipill	99%/90-97%	To be taken daily at the same time. Thickens cervical mucus to block sperms.
Monthly injectables or Combined Injectable Contraceptives (CIC)	99/97%	Irregular vaginal bleeding
Progestogen-only injectables	99/97%	Irregular vaginal bleeding; delayed return to fertility after use.
Intrauterine Device (IUD) – levonorgestrel		Thickens cervical mucus. Amenorrhea.
Intrauterine Device (IUD)-- copper-containing	>99%	Copper component damages sperms.
Male sterilization (vasectomy)	>99% after 3-months semen evaluation; 97-98% without semen evaluation	Surgical intervention. Permanent contraception by cutting vas deferens tubes.
Lactational Amenorrhea (LAM)	99/98%	Effective as long as monthly bleeding has not yet returned. Requires exclusive breastfeeding day and night of infant less than 6 months old.
Basal Body Temperature (BBT).	99/75%	Fertile phase has passed when body temperature has risen (0.2-0.5° C) and remained such for 3 days. Conception is unlikely from 4th day following rise of temperature until next menstruation.
Symptothermal	98/98%	Measuring of body temperature, observation of cervical mucus (clear texture), and palpation of cervix (soft consistency and opening).
Male condoms	98/85%	Protects against sexually transmitted diseases (STD) including HIV.
TwoDay	96/86%	Coitus is avoided during fertile days. Fertile phase is tracked by observing presence of cervical mucus (color and consistency). Unprotected coitus may resume after 2 consecutive dry days or absence of secretion.
Withdrawal	96/73%	Timing of withdrawal is difficult. Risk of ejaculation inside vagina.
Standard Days (SDM)	?/88%	Fertile period is tracked and coitus avoided (usually days 8-19 of each 26-32 day cycle).
Calendar (rhythm)	91/75%	Monitor pattern of menstrual cycle over at least 6 months. Subtract 18 from shortest cycle (this is the estimated first fertile day) and 11 from longest (this is the estimated last fertile day). Caution when drugs are used (anxiolytics, antidepressant, NSAID, or certain antibiotics).
Female condom	90/79%	Barrier to prevent contact between sperm and egg. Protects against sexually transmitted diseases (STD) including HIV.

A comparison of this WHO table with the FDA survey shows not only a loss of precision in the latter but also a lack of several internationally recognized methods which are listed in the WHO table as Basal Body Temperature, Symptothermal, TwoDay, Standard Days, and Calendar (rhythm). These methods are also included in most international rankings and especially in the above cited Contraceptive Technology CT Failure Table [6]. According to this table, one of the fertility awareness-based methods achieves a perfect use estimate of 0.4, which indicates an efficacy almost as high as combined pill and progestin-only pill (perfect use estimate of 0.3).

As can be seen in a comparison of the various tables, surveys and charts presented in the past, there are essential disparities concerning data on efficacy and adverse events caused by drugs, especially drug interaction. Above all, the focus is on efficacy and questions of safety remain open. It is to be feared that owing to these deficits in information, some women might consider the presently available tables as unreliable. What might be an even more perilous consequence, they might refrain from using a contraceptive method, increasing in this way the risk of an unintended pregnancy and perhaps even an abortion.

RESULTS AND CONCLUSIONS

The foregoing discussion brings to light unresolved questions and underscores the need for an intensified pharmacological inquiry into several aspects of contraception, especially safety and mechanisms of action of the various drugs and hormones administered in family planning and birth control. The most important finding is the need for continued research on adverse events and the possibility of reducing or avoiding them. Also, the needs of women with intolerance to hormones and devices should be taken seriously and their preference for non-hormonal contraception honored. Reliable unadulterated information in the form of comprehensive tables might motivate an additional number of women to engage in contraceptive pursuits.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest.

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