Acta Scientific Pharmacology

Volume 2 Issue 9 September 2021

Research Article

The Need for Intensified Pharmacovigilance in the Pharmacology of Contraception

Kurt Kraetschmer MD, PhD*

Department of Reproductive Medicine, Austrian American Medical Research Institute, Austria

***Corresponding Author:** Kurt Kraetschmer, Department of Reproductive Medicine, Austrian American Medical Research Institute, Austria.

Received: July 19, 2021

Published: August 24, 2021

Abstract

The research article aims at determining as to whether or not pharmacovigilance accomplishes its objective to reveal adverse events and other unresolved problems in the pharmacology of contraception. To make this determination a critical method is applied which analyses publications of high impact research, information material emanating from the most influential health agencies, and documents disseminated by market-leading pharmaceutical companies. An analysis of the findings by pharmacovigilance in various areas pertaining to contraception shows that numerous unresolved problems still await a solution. Consequently, the article argues that pharmacovigilance has to intensify its efforts to bring to light adverse events that pose a threat to the health of women using contraceptive products.

For the intensification of pharmacovigilance, it is suggested that efforts be increased in three areas: research, marketing, and clinical practice. For researchers investigations in pharmacovigilance should be made as attractive as research topics suggested by pharmaceutical companies which promise financial remunerations for promoting their products in research publications. Manufacturers should pay heightened attention to post-marketing experiences and peruse them for the amelioration of their products. In the clinical practice grievance mechanisms should be implemented which allow instant and effective reports about adverse events or harm experienced.

Keywords: Contraception, Pharmacovigilance; Pharmacology; Hormones

Background and Aim

The role of pharmacovigilance (PV), as defined by the WHO "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem" has been described in various areas but so far not in the pharmacology of contraception. The present article aims at filling this lacuna and argues that intensification of PV is essential for the advancement of knowledge and the protection of consumers. On the background of pharmacological findings pertaining to contraception on the one hand and repeated reports about severe injuries to women using contraceptive products on the other, the article aims at elucidating the importance of intensifying PV in order to ameliorate the safety of contraceptive methods.

Materials and Methods

The material used comprises pertinent research articles, clinical reports, news media, publications by pharmaceutical companies (package information leaflets, information for the user, patient

information leaflets, packaging labels, consumer leaflets, etc.) and health agencies, as well as reliable internet sites. The method employed is a critical analysis which subjects the relevant scientific literature to a scrutiny whose aim is to reveal lacunae in present-day knowledge, demonstrate the contradictory character of doctrines, and highlight flawed science disseminated through various channels. The bench mark of this analysis is the fundamental ethical principle "nil nocere", i.e. do not harm.

Results

Pharmacovigilance has been defined only in general terms by the WHO and other institutions. According to that part of the WHO definition which speaks of "any other medicine/vaccine related problem" it appears that PV should be omnipresent in research on drugs. In the pharmacology of contraception there are in fact numerous problems not yet resolved. PV has not yet clarified controversies about emergency contraception, such as regimen and the restriction to a "back-up" method. Also, the mechanism of action with regard to fertilization as opposed to implantation has not yet been clarified.

The lack of auto-control mechanisms in PV has been brought to light by the detrimental economic ramifications of an intratubal implant which had been withdrawn from the market by the manufacturer after it had caused severe harm to thousands of women worldwide. It appears that the FDA as a fundamental component of PV has not implemented internal control mechanisms to assure timely and efficient reaction to complaints by users. In the area of non-hormonal methods, PV has so far not intervened to avert the dissemination of flawed science which at this moment is going rampant by internet sites presenting a multitude of tables concerning the efficacy of contraceptive methods.

Discussion

The pharmacology of contraception has advanced knowledge on several topics, such as synthetic estrogens, progestational agents, oral contraceptive pills with varying contents of estrogen and progesterone, Long-Acting Reversible Contraception (LARC), as well as surveys of the efficacy of contraceptive methods. Pharmaceutical companies have benefited from this knowledge and contributed to the emergence of a world market for contraceptive products which presently constitutes a multibillion business.

Various products for contraception have brought not only benefits for their users but also threats to the safety of thousands of women worldwide. The risks for the health of women pursuing contraception and birth control are causally related to various adverse events and complications, such as ectopic pregnancy, thromboembolic events, migrations of an implant to the pulmonary artery, dislocation of an intrauterine device, allergic reactions, streptococcal infections, and others [1]. The following discussion aims at showing how pharmacovigilance should further improve the quality of contraceptive products and the safety of their users. In a first step, the discussion presents the most essential insights of contraceptive pharmacology including controversial issues pertaining to Emergency Contraception (EC); in a second step shortcomings and weaknesses of pharmacovigilance are analysed; and finally, the role of pharmacovigilance in non-hormonal contraception is outlined.

Topical issues and physiological insights in the pharmacology of contraception

At the core of research in the pharmacology of contraception are the two hormones regulating the menstrual cycle, estrogens and progesterone. The naturally occurring estrogens are C17 steroids, namely 17beta-estradiol, estrone, and estriol. In their biosynthetic pathway they are formed from androgens, and in the circulation they are formed by aromatisation of androstenedione. The enzyme aromatase catalyses the reaction of androstenedione to estrone and the conversion of testosterone to estradiol. In the circulation 17beta-estradiol, the primarily secreted estrogen, is in equilibrium with estrone. Estrone is further metabolized to estriol, "probably for the most part in the liver" [2]. The most potent estrogen of the three is estradiol, the least potent is estriol.

Concerning synthetic estrogens, the ethinyl derivative of estradiol is a potent estrogen and - in contrast to naturally occurring estrogens - is active when administered orally, "because it is resistant to hepatic metabolism" [2]. Diethylstilbestrol, a non-steroidal estrogen used for the treatment of menopausal as well as post-menopausal disorders, and several related compounds are assumed to be estrogenic because they are converted to a steroid-like ring structure in the body.

Progesterone, a C_{21} steroid, is secreted by the corpus luteum, the placenta, and in small amounts by the ovarian follicle. In all tis-

sues that secrete steroid hormones, it is an important intermediate. Small amounts of progesterone seem to enter the circulation from the testes and the adrenal cortex. It also seems that 17alpha hydroxyprogesterone is secreted together with estrogens from the ovarian follicle. Progesterone has a short half-life, and in the liver it is converted to pregnanediol, "which is conjugated to glucuronic acid and secreted in the urine" [2].

For contraceptive purposes with natural methods and for fertility treatments, two properties of progesterone must be emphasized, namely its thermogenicity and its ability to stimulate respiration. "Progesterone is thermogenic and is probably responsible for the rise in temperature at the time of ovulation. It stimulates respiration, and the alveolar P_{CO2} (P_{ACO2}) in women during the luteal phase of the menstrual cycle is lower than that in men" [2]. During pregnancy the decline in P_{ACO2} parallels the rise in progesterone secretion. The thermogenic property of progesterone is the basis for so-called temperature method as well as for the symptothermal method, the most effective among the fertility-awareness based methods. The stimulation of respiration through progesterone at the time of ovulation has been used within the framework of fertility treatments for the development of a device which allegedly indicates with high precision the point in time when ovulation occurs and chances for conception are optimal [3,4].

Traditionally, for oral contraception an orally active estrogen, as for example ethinyl estradiol, is combined with a synthetic progestin such as norethindrone. Similar to ethinyl estradiol norethindrone has an ethinyl group on position 17 of the steroid nucleus, which makes it resistant to hepatic metabolism. Presently it is established that small as well as large doses of estrogen are effective contraceptives. Small doses have the advantage of reducing the risk of thromboses and other complications. Progestin alone can be used for contraception, but it is more effective when used in combination with estrogens. Progestin is used also for implants and can prevent pregnancy for up to five years.

In an attempt to classify the various possibilities of contraception, a distinction has been made between hormonal contraception with inhibition of ovulation and hormonal contraception without inhibition of ovulation [5]. Hormonal contraception with inhibition of ovulation comprises the following: one phase (> 50 µg estrogen) hormones; one phase low hormone, i.e., micropill (< 50 µg estrogen and low gestagens, e.g. 150 µg levonorgestrel or desogestrel); two phases with estrogens in the first phase and gestagens in the second phase; two step step-up pills with gestagens already during the first phase; three step pills with different doses of estrogens plus gestagens adapted to the normal cycle; and finally, parenteral gestagen depot injection. Hormonal contraception without inhibition of ovulation can be accomplished by the minipill - (initiated in 1965) with the use of small doses of gestagens, e.g. 30 µg levonorgestrel [5].

Intrauterine devices - products made out of metal or plastic - are frequently used to control population growth but their mechanism of action is still unsettled. At least those containing copper seem to have a spermicidal effect. "Their usefulness is limited by their tendency to cause intrauterine infections" [2]. In addition to ascending infections, expulsion is a highly feared complication [6]. Intrauterine devices together with implants belong to the so-called Long Acting Reversible Contraception (LARC), and these forms of contraception are considered the most effective [7]. Due to their high estimates for efficacy, they are recommended for all women. "IUDs and hormonal implants are safe for almost all women, including adolescents, as well as women in the postpartum or postabortion period" [7].

Despite the commonly accepted importance of effectiveness, this author argues that effectiveness is but one parameter for ranking and rating contraceptive methods. Other parameters are safety, continuation of use, and convenience. If convenience is prioritized in a ranking, then attention has to be drawn to one of the hormonal methods which has received increasing interest during the recent years, namely Emergency Contraception (EC) [8].

Challenges for pharmacovigilance posed by emergency contraception (post-coital contraception)

This author claims that EC should be considered as one of the most noteworthy forms of present-day contraception due to its convenience and effectiveness. Since EC is the last chance to avoid pregnancy it could be designated also as "ultima ratio contraception". Traditionally known as the morning-after pill, emergency contraception has raised interest because it avoids the problem of compliance, i.e., daily administration of pills. The reduced administration of pills, namely just two pills within 12 hours, can be viewed as the primary benefit of EC.

Besides ulipristal acetate as one of the most recently advocated

options for EC, there are other pills available, and they have been divided into three types, namely combined Emergency Contraception Pills (ECPs) containing both estrogen and progestin; progestin-only ECPs; and ECPs which contain an antiprogestin (either ulipristal acetate or mifepristone). Presently, progestin-only ECPs have replaced the older combined ECPs "because they are more effective and cause fewer side effects" [8].

Concerning efficacy, the antiprogestin ulipristal acetate (30 mg in a single dose) is considered to be the most effective pill for EC in the United States and Europe (cf. Figure 1), and estimates of its effectiveness range "from 62% to 85%" [8].

Figure 1: Ulipristal acetate [9].

Figure 1

If intrauterine devices are employed for EC, the efficacy is even higher, namely 0.2 (perfect and typical use) for Mirena (levonorgestrel); and 0.6 (perfect use) and 0.8 (typical use) for ParaGard (copper T) [10].

Concerning the two forms of IUDs, copper-containing and levonorgestrel-containing, it should be noted that the latter have been studied extensively for use as EC. The active ingredient in Mirena has been indicated by the manufacturer as "levonorgestrel USP, (-)-13-Ethyl-17-hydroxy-18,19- dinor-17α-pregn-4-en-20-yn-3-one" [11]. It has a molecular weight of 312.4 and the molecular formula C21H28O2. Concerning the use and administration of this IUD, it has been emphasized that the release rate decreases from 20 µg/day to 10 µg/day in the course of 5 years. "Mirena contains 52 mg of levonorgestrel. Initially, levonorgestrel is released at a rate of approximately 20 µg/day. This rate decreases progressively to half that value after 5 years" [11]. It should be noted that as early as 2017 criticism has been voiced by news media due to severe side effects of Mirena, but it is not known whether PV has provided clarification of the issues [12].

Concerning comments on the efficacy of pills for EC, attention must be drawn to the WHO table of 2017 [13] which indicates an estimate of 99% efficacy. Along the same line, German research argued as early as 2000 that the efficacy of EC by means of "interceptive pills" in case of perfect use is as effective as 99% [6]. This research, which ranks contraceptive methods according to the Pearl Index (PI), explains the mechanism of action in such a way that the morning-after pill interrupts the synchronisation between blastocyst development and endometrial preparedness for nidation. At the time of the publication of this research, the regimen for interception was 4 pills (50 µg ethinylestradiol and 0.25 mg levonorgestrel) taken within 60 hours: 2 taken within 48 hours of unprotected cohabitation and the remaining 2 taken after an interval of 12 hours.

As mentioned above, the efficacy of ulipristal acetate [8] has been particularly underscored as the highest among ECPs, and numerous publications have reiterated this claim. However, the reliability of this claim is by no means ascertained because a preventive therapy requires different statistical approaches. Such a therapy, it is hypothesized from a statistical perspective, is best evaluated by comparing the probability that the condition will occur if the therapy is implemented to the probability that it will occur without such implementation. The chance that pregnancy would occur without implementation of emergency contraception is estimated indirectly using published data on the probability of pregnancy on each day of the menstrual cycle. This estimate is compared to the actual number of pregnancies observed after treatment in observational treatment trials. "Effectiveness is calculated as 1-O/E, where O and E are the observed and expected number of pregnancies, respectively. Calculation of effectiveness, and particularly the denominator of the fraction, involves many assumptions that are difficult to validate" [8].

As can be seen, the frequently encountered uncritical claims about effectiveness must be taken with caution. PV should clarify such claims and address also other issues with respect to EC, namely the statement that EC is merely a "back-up" method, the recommendation concerning dose, and the time interval for effective implementation of EC.

This author hypothesizes that for women whose sexual activity is limited to just one cohabitation per month or even less it seems justifiable to ignore the advice given by most health agencies and clinics which recommend implementation of a "primary method" of contraception. "The morning-after pill is intended for back-up contraception only, not as a primary method of birth control. Morning-after pills contain either levonorgestrel (Plan B One-Step, Aftera, others) or ulipristal acetate (ella)" [14].

In addition, this author also suggests to draw consequences from research which shows that administration of the pills has to take place within 120 hours. Furthermore the dose to be administered must not be the one recommended commonly, as research has shown that a higher dose administered once is as effective as a lower doses administered twice: "However, studies have shown that a single dose of 1.5 mg is as effective as two 0.75 mg doses 12 hours apart" [8].

The most problematic topic in EC is the explanation of the mechanism of action. The most commonly embraced assumption holds that combined ECPs containing the estrogen ethinyl estradiol and the progestin levonorgestrel can inhibit or delay ovulation. "This mechanism of action may explain ECP effectiveness when used during the first half of the menstrual cycle, before ovulation has occurred" [8]. Among other possible mechanisms are " interference with corpus luteum function; thickening of the cervical mucus resulting in trapping of sperm; alterations in the tubal transport of sperm, egg, or embryo; and direct inhibition of fertilization" [8]. An additional mechanism could be the intrauterine concentrations of glycodelin. On the basis of a study where levonorgestrel was administered previously to the Luteinizing Hormone (LH) surge and increased the intrauterine concentrations of glycodelin at the time of ovulation it has been hypothesized: "since glycodelin inhibits fertilization, this result may indicate an additional mechanism of action when ovulation is not inhibited" [8].

In explaining the mechanism of action efforts are made to disprove the crucial claim regarding abortogenicity. Thus, clinical information material for patients emphasizes the absence of any abortifacient effect of EC: "Keep in mind that the morning-after pill isn't the same as mifepristone (Mifeprex), also known as RU-486 or the abortion pill. This drug terminates an established pregnancy - one in which the fertilized egg has attached to the uterine wall and has begun to develop" [14]. Regarding levonorgestrel, it should be emphasized that it is merely in vitro observations that have led to assumptions concerning the attachment of an embryo to the uterine wall: "Levonorgestrel does not impair the attachment of human embryos to an in vitro endometrial construct and has no effect on the expression of endometrial receptivity markers" [8]. In order to buttress this claim, reference has been made to medical authorities such as the United States Food and Drug Administration/National Institutes of Health and the American College of Obstetricians and Gynecologists to draw a lapidary conclusion: "Therefore, ECPs are not abortifacient" [8]. From the perspective of PV the question must be raised why these institutions are considered as "authorities" in view of the topic which belongs to scientific research and not to areas of public health. From a physiological perspective it seems clear that a pregnancy begins when a new life comes into existence, namely as soon as a sperm penetrates an oocyte. "At that time the second polar body is cast off and the fertilized ovum proceeds to form a new individual" [2]. The task for PV in this controversy about the beginning of pregnancy would be to clearly distinguish between scientific observations and hypothetical conventions proposed within the framework of public health.

Shortcomings and accomplishments of PV

Besides EC, other areas pose challenges for PV, and it appears that numerous open questions still await an answer, such as the topic of interactions of drugs. In addressing this topic one must consider its complexity due to an ever-increasing number of drugs on the market. Recently, in 2020, a study has drawn attention to difficulties encountered in drug interaction studies for contraception. "These include the role of new molecular entity properties with respect to whether they are teratogens, selection of progestins and their different metabolic pathways, choice of PK- or PK/pharmacodynamic (PD)-based study design and assessment on whether drug interaction findings with one oral contraceptive can be generalizable to other oral contraceptives" [15].

An ongoing task for PV is the rectification of misleading information disseminated through various channels. Thus, frequently encountered uncritical claims that oral contraceptive pills are reliable and safe without reference to the well-known side effects can easily mislead prospective users. "Oral contraceptives, also called birth control pills, are a safe and reliable option for preventing unwanted pregnancy" [16].

Concerning the task of PV to identify adverse events, attention must be drawn to the complexity of physiological processes involved in the pharmacokinetics and pharmacodynamics and the difficulty of implementing effective methods for their observation. Already during the last century it has been claimed that the vital processes belonging to female reproduction are difficult to study by scientific techniques: "Except for methods which demonstrate ovulation, there is a lack of suitable techniques for convenient study in women of other functional steps in the reproduction process, such as ovum release, fertilization, egg and blastocyst migration, tubal motility, nidation, spermatozoal migration and capacitation" [17].

One of the serious shortcomings of pharmacovigilance is the paucity of attention paid to quantitative studies, especially to the validity of statistical methods. This lack should be remedied because such studies show the preferences of the consumer and allow to draw inferences concerning safety and convenience. Thus, in a study of 2015 it has been found that oral contraceptive drugs still dominate the market although one might hypothesize that the convenience of implants should have had a noteworthy impact on sales of oral contraceptive pills. In this study on the contraceptives dispensed in Ireland oral contraceptives were identified as the most preferred. "Of all contraceptives dispensed in 2013, oral contraceptives were used the most (74%) and long acting reversible contraceptives (LARCs) the least (7.5%) [18].

One of the shortcomings of PV -- which could be defined as an auto-control deficit -- came to light in conjunction with reports about serious threats to the health of women using an intratubal implant for contraception. "First approved for contraceptive use in 2002, Essure is a device that is implanted through the cervix and into the fallopian tubes. The device consists of 2-inch-long metal coils, around which scar tissue builds to form a barrier to stop sperm from fertilizing eggs" [19]. In 2018, this device for permanent contraception had given rise to thousands of complaints and lawsuits [20], and two years later, in 2020, the manufacturer agreed to pay $1.6 billion to resolve most of the US litigations. In addition it turned out that thousands of complaints of injuries had not been reported to the FDA [21].

Concerning the adverse events causally related to this product it can be hypothesized that PV should have reacted earlier. The FDA waited obviously too long before it reacted to complaints by women who had already experienced severe harm. The FDA's reaction, moreover, was not stringent enough because it requested only documentation to the effect that women had been informed appropriately about adverse events. Finally, it was the company's own decision to withdraw its product and not an ordinance by the FDA.

Notwithstanding the shortcomings discussed above some accomplishments by PV must be acknowledged. Among these achievements are findings in oncology, in ophthalmology and in psychiatry. Recently, the probability of leukemia in children born to mothers who had used hormonal contraception has been explored by research in oncology [22]. In 2018, the European Medicines Agency (EMA) confirmed the danger of suicidal action in association with hormonal contraception [23]. Research in PV drew attention to the possibility of glaucoma and oral hormonal contraceptives have been identified as causally related to increased intraocular pressure and the associated risk of blindness: "The association between female sex hormones and intraocular pressure (IOP) changes has long been known. However, reports on the increased risk of open-angle glaucoma in females taking oral contraceptive pills for three years or more is a recent finding, which requires further studies to probe the causal association between estrogen, progesterone, and rise in IOP" [24].

The task of PV - according to this author -- consists not only in uncovering unnoticed harmful effects, but also in drawing consequences to protect the consumer. For this purpose PV should assess the communication between consumer and manufacturer concerning adverse events, risks, and complications. This assessment should include all documents generated by manufacturers for their customers, ie, information for the user, instructions for use, or packaging labels. Unfortunately, owing to incomplete and inaccurate data, these documents do not always stand up to standards of well-established medical ethics, in particular to the principle of informed consent as specified by the American Medical Association. According to this principle, each patient should obtain sufficient information to be able to "make an intelligent choice" [25]. The ability to make an intelligent choice can be warranted only if information provided by the manufacturer is complete, comprehensible and comprehensive. Alas, manufacturers do not always pay sufficient heed to such requirements [26], and PV should intervene to assure that manufacturers meet the standards required by medical ethics.

In the face of adverse events, risks, and complications of hormone-containing products, it seems understandable that a grow-

ing number of women is turning to non-hormonal contraception. In fact, an emerging popularizing medical literature voices the criticism of women who consider themselves as the victims of hormonal contraception and give testimony of their satisfaction with non-hormonal methods [27].

Nonhormonal methods of contraception and the role of PV to rectify error-prone information

At present, non-hormonal methods are commonly designated as "fertility-awareness based" methods, although the traditional terminology "natural family planning methods" seems more appropriate, as it underscores the essential feature, namely "natural" as opposed to "artificial", ie, "hormonal". In the past, numerous sources of information, including the Centers for Disease Control (CDC), have disseminated error-prone information on these methods and have neglected in particular the estimates for efficacy in case of perfect use. Due to this neglect these methods have been discredited as the least effective of all contraceptive methods [28] or have been excluded altogether from surveys of contraceptive methods [29].

In the face of such erroneous notions, PV should investigate the importance of estimates for the efficacy of perfect use, which is frequently considered unattainable and less relevant than typical use. In particular PV could substantiate claims made by Contraceptive Technology [10] and German research [6] which hold that the most effective of these methods, the symptothermal method has a perfect use efficacy superior to oral contraceptives, namely 0.4. Regarding these methods PV could address also the importance of the parameter safety as opposed to efficacy. This distinction is frequently disregarded in the literature, and the term "safe" is used as a synonym for efficient. Regarding safety it is generally accepted that natural methods have to be ranked highest if an attempt is made to rate and rank methods. As a result of efforts to rank methods in the form of a synoptic overview the so-called Safety-Efficacy-Convenience Rating has been proposed [30], which should prove particularly useful for the clinical practice where women's interest focuses on individual safety in the sense of precision, ie, personalized, medicine.

In the face of erroneous notions concerning contraceptive methods, PV should also analyse the advantages and disadvantages of new definitions and taxonomies introduced by research such as Contraceptive Technology. In fact, these methods have been redefined and simplified although their basic assumptions have remained valid. Thus Contraceptive Technology [10], one of the most trustworthy research on contraception, has presented the traditional methods under a new taxonomy, i.e. "Fertility-Awareness Based" methods and with a new terminology: Ovulation, Two-Day , Standard Days, and Symptothermal. Another commonly used designation for these methods is Periodic Abstinence, a nomenclature which adequately draws attention to the pivotal requirement for successful implementation of the methods, ie, abstinence or use of a barrier method during the fertile days [31]. Concerning abstinence it should be mentioned that this strategy has been recognized also as the most effective protection against Sexually Transmitted Diseases (STD) by the US FDA: "Except for abstinence, latex condoms are the best protection against HIV/AIDS and other STIs" [29].

Eradication of error seems particularly important in light of developments in internet sites where a steadily growing number of tables and overviews of contraceptive methods make their appearance. Data presented in these charts and tables, which are accessed by a great number of internet users, frequently lack scientific verification. It must be feared therefore that this kind of information is prone to misleading instead of enlightening prospective users of contraceptive methods.

Conclusions and Implications

As the need for intensified PV in the pharmacology of contraception has been demonstrated, possibilities for such intensification have to be probed. This author suggests that efforts be increased in three areas: research, post-marketing, and clinical practice. Researchers should be motivated by incentives to address issues of PV with the same interest as topics associated with financial gains offered by manufacturers in return for promotion of their products. Manufacturers should pay increased attention to post-marketing experiences and peruse them for improving the safety of their products. In the clinical practice grievance mechanisms should ascertain immediate and effective communication with manufacturers to report hitherto unknown side effects experienced by users.

Bibliography

1. Kraetschmer K. "IIs Contraception Really Safe?" *International Journal of Sexual and Reproductive Health* 1.1 (2019): 1-11.

2. Ganong WF. "Review of Medical Physiology". East Norwalk, Connecticut: Prentice-Hall International Inc. (17th ed.) (1995).

3. Moeller K-T., *et al*. "Exspiratorische CO2-Messung in der Zyklusüberwachung - ein einfacher und zuverlässiger Marker zur Bestimmung der fertilen Tage". *Journal für Fertilität und Reproduktion* 13.1 (2013): 7-12.

4. Breath ilo Zyklustracking (2021).

5. Pschyrembel. "Klinisches Wörterbuch". Berlin: Walter de Gruyter (256th ed.) (1990): 888.

6. Gröger S and Grüne B. "Kontrazeption". In: Diedrich K, ed. Gynäkologie and Geburtshilfe. Berlin: Springer (2000): 60-87.

7. Curtis KM and Peipert JF. "Long-Acting Reversible Contraception". *The New England Journal of Medicine* 376 (2017): 461-468. DOI: 10.1056/NEJMcp1608736.

8. Trussell J., *et al*. "Emergency Contraception: A Last Chance to Prevent Unintended Pregnancy June". Office of Population Research, Princeton University, Princeton NJ 08544, USA (2017).

9. "Ulipristal acetate" (2021).

10. Trussell J. "Contraceptive efficacy". Table 3-2. In: Hatcher RA, Trussell J, Nelson AL, Cates W, Kowal D, Policar M. Contraceptive Technology: Twentieth Revised Edition. New York, NY: Ardent Media (2011).

11. Bayer Information. Mirena. Patient information booklet, July 2008. Bayer HealthCare Pharmaceuticals Inc. All rights reserved. component codes July. Wayne NJ (2008).

12. Mirena. Bayer-Hormonspiralen Mirena, Jaydess, Kyleena: Psychisch (2017).

13. "WHO – Family Planning/contraceptive methods" (2020).

14. Mayo Clinic. "Morning-after pill" (2021).

15. Myong-Jin Kim and Venkateswar Jarugula. "Clinical Pharmacology in Women's Health: Current Status and Opportunities". *The Journal of Clinical Pharmacology* 60.2 (2020): S7-S10.

16. "Oral Contraceptives". *Clinical Pharmacy and Pharmacology* (2021).

17. RudelHW. "Pharmacology of oral contraceptives". *Clinical Obstetrics and Gynecology* 11.3 (1968): 632-644.

18. Laura O'Mahony., *et al*. *British Journal of Clinical Pharmacology* 80.6 (2015): 1315-1323.

19. "Expert Institute" (2021).

20. Washington Post (2018).

21. Washington Post. Bayer did not report thousands of Essure complaints to FDA (2020).

22. Hargreave M., *et al*. "Maternal use of hormonal contraception and risk of childhood leukaemia: a nationwide, population-based cohort study". *The Lancet Oncology* 19.10 (2018): 1307-1314.

23. Gènéthique - Contraceptive pill: European Medicines Agency demands warnings about the risk of depression and suicide. Publié le: 10 (2018).

24. Bhanwra S and Ahluwalia K. "The association of oral contraceptive pills with increase in intraocular pressure: Time for pharmacovigilance to step in". *Journal of Pharmacology and Pharmacotherapeutics* 6.1 (2015): 51-52.

25. Code of Medical Ethics. Current Opinions. American Medical Association. Chicago, Illinois (1992).

26. Kraetschmer K. "Topical Issues in Translational Pharmacology and Pharmaceuticovigilance: Can Pharmacological Research on Birth Control and Contraception Meet the Requirements of Bioethical Standards?" *Journal of Pharmaceutical Sciences and Pharmacology (*2019): 87-104.

27. Morelli I. Kleine Pille, grosse Folgen. Kleine Pille, große Folgen: Wie Hormone dich krank machen (2021).

28. Centers for Disease Control and Prevention (CDC) (2017).

29. Kraetschmer K. "Can Ratings of Contraceptive Methods Motivate Women to Engage in Family Planning and Birth Control? A Review". *Journal of Gynecology and Women's Health* 11.4 (2018): 555817.

30. Food and Drug Administration (FDA) Approved Methods of Birth Control (2013).

31. Beers MH and Berkow R. (editors) MSD Manual. Whitehouse Station, N.J. USA: Merck and Co. Inc. (17th ed.) (1999).

Volume 2 Issue 9 September 2021