Acta Scientific Pharmacology

Volume 4 Issue 1 January 2023

Review Article

Pharmacological, Medical, Legal, and Ethical Aspects of Emergency Contraception by Means of Ulipristal Acetate

Kurt Kraetschmer*

MD, PhD, Austrian-American Medical Research Institute, Vienna, Austria

***Corresponding Author:** Kurt Kraetschmer, MD, PhD, Austrian-American Medical Research Institute, Vienna, Austria.

Received: November 24, 2022

Published: December 19, 2022

Abstract

Background and Aim: On the background of claims that ulipristal acetate is the most effective hormonal medication for emergency contraception, the critical analysis investigates the pharmacological, medical, legal, and ethical aspects of this medication. The aim is to illuminate critical issues not yet sufficiently explored in research on emergency contraception.

Method and Material: The method is a critical analysis which assesses present knowledge contained in pertinent high-quality publications. The material encompasses articles published in high-ranked scientific journals and information disseminated by the most influential health agencies, such as the US Food and Drug Administration, the World Health Organization, the American College of Obstetricians and Gynecologists, and the American College of Pediatricians.

Results: The analysis of pharmacological aspects of ulipristal acetate shows that its similarity to mifepristone raises the question regarding abortifacient potentials of ulipristal acetate. The analysis of medical aspects of ulipristal acetate reveals that adverse events are not sufficiently described and that statistical methods for determining efficacy need to be refined. The analysis of legal aspects suggests that legislation on abortion medication might be relevant not only for mifepristone but also for ulipristal acetate. The analysis of ethical aspects unveils that the physiological processes of fertilization and implantation are crucial in discussions on the beginning of human life.

Conclusions and Implications: Concerning pharmacology it seems advisable to continue research on the mechanism of action of ulipristal acetate not only as a contraceptive but also as a contragestive. Concerning medical research, the efficacy of ulipristal acetate as a preventive therapy should be investigated with increased statistical verifiability. The results of these investigations should be communicated comprehensibly to the patient. Concerning legal aspects, the suitability of ulipristal acetate as abortion medication should be discussed on the basis of findings in human physiology. Concerning ethical debates the question of the beginning of life should be based on scientific insights into the physiological processes of ovulation, fertilization, and implantation.

Keywords: Contraception; Abortion; Pharmacology; Medicines; Ethics

Introduction

Emergency contraception, better designated as post-coital or post-cohabitation contraception, can be defined as a preventive therapy used to avoid pregnancy subsequent to unprotected or inadequately protected sexual intercourse. Some of the most common indications for emergency contraception include contraceptive failure (e.g. condom damage or omitted administration of oral contraceptives) and failure to use any form of contraception. Oral emergency contraception was first

described in the medical literature in the 1960s. "The U.S. Food and Drug Administration (FDA) approved the first dedicated product for emergency contraception in 1998. Since then, several new products have been introduced" [1].

At present, Emergency contraception (EC) can be administered in a variety of formats, namely first in a non-hormonal fashion by means of a copper-containing intrauterine devices (IUD), second by means of a copper intrauterine contraceptive system releasing ulipristal acetate, and third through Emergency Contraceptive Pills (ECPs), i.e.

- Ulipristal Acetate (UPA) taken as a single dose of 30 mg.
- Levonorgestrel (LNG taken as a single dose of 1.5 mg or – alternatively – LNG taken in two doses of 0.75 mg each, 12 hours apart.
- Combined oral contraceptive pills (COCs), taken as a split dose, one dose of 100 µg of ethinyl estradiol plus 0.50 mg of LNG, followed by a second dose of 100 µg of ethinyl estradiol plus 0.50 mg of LNG 12 hours later. (Yuzpe method).

Concerning the copper contraceptive system releasing ulipristal acetate, a study of 2021 aimed at assessing pharmacodynamic and pharmacokinetic outcomes of a novel copper (Cu) intrauterine system (IUS) releasing ulipristal acetate in healthy women. The implications of this study emphasized three benefits, namely reduced bleeding, low incidence of endometrial changes, and the absence of serious adverse events. In addition, a non-contraceptive advantage especially for women with low hemoglobin was found: **"**The preliminary results of this short-term study of a novel copper intrauterine system (IUS) delivering ulipristal acetate showed reduction of bleeding, low incidence of progesterone receptor modulator associated endometrial changes, and absence of serious adverse events. By preventing copper-induced increase in bleeding, this IUS could provide a noncontraceptive benefit, especially for women with low hemoglobin" [2].

Among the pills administered for EC, ulipristal acetate has been described as being the most effective: "The evidence suggests that ulipristal acetate is a more effective form of emergency contraception than levonorgestrel. Ulipristal acetate is twice as likely as levonorgestrel to prevent pregnancy when used within 72 hours or within five days of unprotected intercourse. When taken within the first 24 hours after intercourse, it reduces unplanned pregnancies by two-thirds when compared with levonorgestrel" [3]. Given the superior efficacy of ulipristal acetate compared with Levonorgestrel and its analogous safety, it is now considered as a first choice hormonal medication for EC: "Ulipristal acetate (UPA) is now recommended as first choice hormonal emergency contraception (EC), due to its higher efficacy and similar safety compared to Levonorgestrel" [4].

Pharmacological aspects of ulipristal acetate as an emergency contraceptive

Pharmacological characterizations of ulipristal acetate are presented in numerous publications. The molecular formula of ulipristal acetate is $C_{30}H_{37}NO_4$.The chemical structure depiction of ulipristal acetate is reproduced in figure 1.

Figure 1: Chemical Structure Depiction of ulipristal acetate [5].

Pharmacological characterizations specify that UPA, an orally bioavailable acetate salt of ulipristal acetate acts as a selective progesterone receptor modulator and has anti-progesterone activity. By binding to the progesterone receptor (PR) ulipristal inhibits PR mediated gene expression and also interferes with progesterone activity in the reproductive system. Owing to this activity ulipristal may inhibit the growth of uterine leiomyomatosis but may also be used as a contraceptive, because it inhibits or delays ovulation and exercises an effect on endometrial tissue. "Furthermore, by inhibiting or delaying ovulation and effecting endometrial tissue, ulipristal can be used as an emergency contraception" [5]. Detailed characterizations of ulipristal as a contraceptive specify

that it can be used as a contraceptive drug due to its property as a progestin and progesterone receptor modulator: "It has a role as a contraceptive drug, a progestin and a progesterone modulator. It is a 3-oxo-Delta(4) steroid, a steroid ester, an acetate ester, a 20-oxo steroid and a tertiary amino compound. It is functionally related to an estradiol" [5]. Descriptions of the pharmacodynamics of UPA explain that tissue targets include the uterus, the cervix, the ovaries and the hypothalamus: "Ulipristal is a selective, reversible progestin receptor modulator and its tissue targets include the uterus, cervix, ovaries, and hypothalamus" [5].

What is of particular importance for ulipristal as an agonist or antagonist is the point in time of the administration, which determines whether follicle growth is delayed, or whether follicular rupture is delayed, or whether endometrial thickness is decreased: "Ulipristal may act as an agonist or antagonist in the presence or absence of progesterone on the tissue target. If given mid-follicular phase, development of the follicle growth is delayed and estradiol concentrations decrease. If given at the time when luteinizing hormone peaks, follicular rapture/sic!/ is delayed by several days. If given early-luteal phase, a decrease in endometrial thickness can be observed" [5]. Regarding metabolism of Ulipristal, the predominant role of CYP3A4 and the minor role of CYP1A2 have been described, along with the metabolites which are either mono-demthylated (active) or di-methylated (inactive). Pertaining to biological half-life, it has been stated: "Mean elimination half-life, single oral dose, healthy subject = 32.4 ± 6.3 hours" [5]. As to the mechanism of action, attention has been drawn to conflicting standpoints. Earlier research studies seem to suggest that the primary mechanism of UPA as EC pill is inhibition or delay of ovulation by suppressing surges in LH. The consequence of this suppression is deferment of follicular rupture. This viewpoint is challenged by more recent investigation which draw attention to a post-fertilization effect. "Conversely, some of the latest investigations pertaining to ulipristal's mechanism of action as an emergency contraceptive propose that it principally elicits its action by preventing embryo implantation, as opposed to preventing ovulation" [5].

Besides pharmacological studies which characterize UA as an EC, information on UPA is available in the manufacturer's description of their product. This information is contained in a package leaflet offering "information for the user" and has been last revised in 2018 [6]. In describing the mechanism of action, the manufacturer states that UPA acts by postponing ovulation due to a modification of the activity of progesterone: "How ellaOne works. ellaOne contains the substance ulipristal acetate which acts by modifying the activity of the natural hormone progesterone which is necessary for ovulation to occur. As a result, this medicine works by postponing ovulation" [6]. Concerning efficacy, the manufacturer claims: "Of 100 women who take this medicine approximately 2 will become pregnant" [6]. With respect to drug interaction, the manufacturer draws attention to 5 medications, namely those for epilepsy (primidone, phenobarbital, phenytoin, fosphenytoine, carbamazepine, oxcarbazepine and barbiturates); those for tuberculosis (rifampicin, rifabutin); those for HIV (ritonavir, efavirenz, nevirapine); and those for fungal infections (griseofulvin) as well as herbal remedies containing John's wort (*Hypericum perforatum*).

As can be seen from the manufacturer's leaflet, it fails to provide complete and comprehensive information, especially on such critical issues, as drug interaction, efficacy, and mechanism of action. Concerning drug interactions, it must be noted that an updated drugbank of 2022 enumerates altogether 10 drugs with a possible interaction with ulipristal acetate, namely Abametapir, Abciximab, Acenocoumarol, Acetaminophen, Acetazolamide, Acetohexamide, Alpelisib, Alteblase, Aminogluthetimide, and Amiodaron [7]. Regrettably, the manufacturer of ella does not mention any of these interactions but limits its enumeration to the drugs mentioned above. Concerning the manufacturer's information on efficacy, it should be noted that the FDA's Birth Control Chart (2021) provides a more modest estimate, stating that 60 to 66% of expected pregnancies could be averted: "Chance of getting pregnant **-** In two large studies, 60 to 66% of expected pregnancies were prevented with correct use of ulipristal acetate" [8]. As can be seen, the FDA's estimate does not harmonize with the estimate indicated by the manufacturer. Of course estimating the effectiveness of a contraceptive for emergency contraception is an ongoing problem and efforts are being made to improve the relevant methods [9]. As illustrated, the manufacturer fails to provide accurate information on drug interaction, on efficacy and on mechanism of action. Concerning drug interactions the manufacturer should have investigated additional drug interactions such as those with dronaderone or other antiarrhythmic drugs. Pertaining to efficacy, the manufacturer's estimate seems exaggerated in light of other publications, such as the one by the FDA. With respect

to the manufacturer's information on the mechanism of action it should be noted that only inhibition of ovulation is mentioned and the critical question of inhibition of implantation remains untold. The manufacturer's failure to provide accurate and comprehensive information constitutes not only a disregard of the consumers right to obtain adequate information; it is also a violation of the ethical principle of informed consent and patient autonomy. These very principles are germane also for an analysis of the medical aspects of UPA as EC. Complete and accurate medical information for the patient must address such issues as mechanism of action, efficacy and safety, i.e, adverse reactions.

Medical aspects of ulipristal acetate as an emergency contraceptive pill

In illuminating medical aspects of UPA as EC attention must be drawn primarily to three topical issues, namely mechanism of action, adverse events, and efficacy. Regarding mechanism of action it should be mentioned that the FDA underlined two possible mechanisms, namely inhibition of ovulation and prevention of implantation through changes of the endometrium: "It works mainly by stopping or delaying the ovaries from releasing an egg. It may also work by changing the lining of the womb (uterus) that may affect attachment (implantation)" [8]. Pertaining to adverse events, the FDA mentions a larger number of side effects than the manufacturer, namely headache, nausea, abdominal pain, menstrual pain, tiredness, and dizziness [8]. Side effects have been described also in a publication on post-marketing experience subsequent to use by over 1 million women. "Commonly reported adverse effects associated with ulipristal acetate in trials included headache, breast tenderness, nausea, and abdominal pain [10]. Likewise, adverse effects have been discussed by addressing the question of method failure, i.e. lack of effectiveness of ulipristal acetate, and only few cases of continuation of pregnancy subsequent to failure of ulipristal acetate have been described in a publication of 2016. "The most frequent adverse effects of ulipristal and levonorgestrel are nausea, headache and dysmenorrhea. There may be intermenstrual bleeding and the next period may be earlier or later than expected. When ulipristal was not effective few women continued with the pregnancy. Data are only available on two women who continued to term. One had a normal live birth and the other had a baby with optic nerve hypoplasia. Ulipristal is excreted in breast milk" [11].

As for efficacy, a publication of 2016 reported the difference in efficacy of UPA depending on the point in time of administration, namely either before or subsequent to ovulation [12]. This study provides extensive information on study outcome measures and on statistics. Concerning study outcome measure the study specifies that the study subjects were at different phases of their menstrual cycle at the time of recruitment. "The primary outcome measure was the percentage of pregnancies prevented (PPP). At the time of recruitment, as subjects were at different phases of their menstrual cycles, their intrinsic risk of pregnancy without EC would differ. Therefore, the PPP was used as a better measure to determine EC effectiveness" [12]. The key concept of the study, the percentage of pregnancies prevented (PPP) was calculated by the following formula:

Concerning the denominator of the equation, Trussell's model was used: "The number of expected pregnancies was determined by the Trussell's model based on the menstrual cycle day of the subjects at the time of UPSI (Trussell., *et al.* 2003)" [12].

$$PPP = \frac{number\ of\ expected\ pregnancies - number\ of\ observed\ pregnancies}{number\ of\ expected\ pregnancies}$$

As regards statistics, the various tests employed were appropriately specified: "Statistics. Categorical variables were compared between the 'pre-ovulatory' and 'post-ovulatory' groups using Fisher's exact test or χ^2 test as appropriate. Continuous variables were compared between the two groups using the Mann–Whitney *U*-test. The two-sided binomial test was used to determine the probability of the difference between the observed and expected pregnancy rates in the respective groups being due to chance. Statistical analyses were performed using MedCalc version 13 (MedCalc Software bvba, Ostend, Belgium) and IBM SPSS Statistics (version 21, IBM Corporation, NY, USA)" [12]. As can be seen from the outcome measures and the statistical tests employed in this study, the question arises as to whether all assumptions can be validated. As early as 2014, authors of a review on emergency contraception drew attention to the difficulty of validating several assumptions. "Calculation of effectiveness, and particularly the denominator of the fraction, involves many assumptions that are difficult to validate. The risk of pregnancy for women requesting ECPs appears to be lower than assumed in the estimates of ECP efficacy, which are consequently likely to be overestimates" [13].

As illustrated in the preceding discussion, an analysis of the medical aspects must address also such critical issues as adverse events, effectiveness, and mechanism of action. While there seems to be general agreement on the former, the latter has not been resolved satisfactorily thus far. After all, the possibility of abortogenesis is not only a medical problem but also a legal and ethical issue.

Legal aspects of ulipristal acetate as emergency contraceptive

One of the ongoing issues in legislations world-wide is abortion, and abortifacient properties of drugs are of pivotal importance in political discussions. Concerning the mechanism of action of UPA it should be noted that an increasing number of publications emphasize similarities between ulipristal acetate and mifepristone, the widely used abortion pill. As early as 2011 a publication drew attention to these similarities and proposed two mechanisms of action for ulipristal acetate, namely contraception and contragestion: "However, ulipristal acetate is structurally similar to mifepristone, and several lines of evidence suggest that a postfertilization mechanism of action is also operative. This mechanism of action is considered to be contragestive versus contraceptive. Ulipristal acetate administration is contraindicated in a known or suspected pregnancy; however, it could quite possibly be used as an effective abortifacient. Health-care providers should inform patients of the possibility of both mechanisms of action with use of this drug" [14]. Likewise, pharmacological comments on the mechanism of action of ulipristal acetate draw attention to post-fertilization effects and hypothesize that the abortifacient potential of the medication might be equal to that of mifepristone. "Regardless, however, considering current and on-going research into ulipristal's ability to prevent embryo implantation, the notion that the medication can elicit post-fertilization effects potentially raises alerts and/or ethical debates over the use of ulipristal owing to potential abortifacient activity, which is considered to be on par or equipotent to that of mifepristone" [5].

As is generally known, mifepristone is a well-established abortion pill used world-wide. In an information document on mifeprix (mifepristone), the FDA stated in 2021: "Mifepristone is approved, in a regimen with misoprostol, to end a pregnancy through 70 days gestation (70 days or less since the first day of a woman's last menstrual period)" [15]. The structure and the physical properties of Mifepristone have been described as a "17-hydroxy-11-(4-dimethylaminophe-nyl)-17-(prop-1-ynyl)-estra-4,9-dien-3-one" [16]. It is derived from the estrane progestins, and has a molecular weight of 429.5. While it is insoluble in water, it rapidly dissolves in the gastric milieu in case of oral administration. For the consumer, it is available in the form of tablets which contain 200 mg of active ingredient. At ambient temperatures it remains stable after three years [16]. The chemical structure of Mifepristone (C29H35NO2) is reproduced in Figure 2.

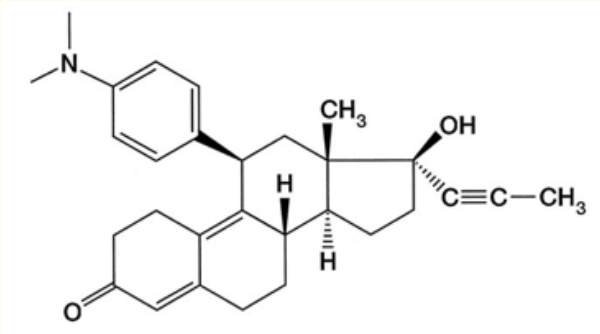

Figure 2: Mifepristone chemical structure [16].

As regards the mechanism of action, the complex of mifepristone with the intracellular progesterone receptor (PR) has been described as down-regulating progesterone-dependent genes. "The complex of mifepristone with the PR inhibits transcription resulting in the down-regulation of progesterone-dependent genes" [16]. In a comparison with other recently synthesized antiprogestins mifepristone appeared primarily as an antagonist with minimal agonist activity. Administration of low doses of pogesterone agonists (PA) in animal experiments showed an antiproliferative effect. Concerning antiproliferative effects, it seemed unresolved whether these were due to a partial progesterone agonistic effect or to an overexpression of the androgen receptor. "As compared with other more recently synthesized antiprogestins, mifepristone is predominantly an antagonist with minimal agonist activity. Several PAs including mifepristone, administered at low doses in the monkey, were shown to exert antiproliferative effects in the endometrium. Whether this effect is due to a partial progesterone agonistic effect, or an overexpression of the androgen receptor is unclear" [16].

In characterizations of mifepristone it has been emphasized that is an orally active synthetic steroid with antiprogesterone and anti-glucocorticoid activities. Emphasis is also placed on

the four indications of mifepristone, which were described in 2004 as follows: "Mifepristone is an orally active synthetic steroid with antiprogesterone and antiglucocorticoid activities. To date, mifepristone is approved in several countries for use in four indications: early termination of pregnancy (TOP), cervical dilatation prior to surgical TOP, preparation for prostaglandin-induced TOP during the second-trimester, and expulsion of a dead fetus during the third trimester" [16]. Besides these four indications mentioned additional indications have been assumed, but research has been contravened due to controversies and philosophical debates. "Although the molecule has several possible indications due to its unique properties, its potential has not been fully realized; the controversy and philosophical debate involving mifepristone has resulted in opposition to further research of this compound" [16]. From a historical perspective it is worth noting that as early as 1985 results have been obtained in studies on RU 486: "RU 486 possesses a high affinity for the progesterone receptor and displays antiprogestational properties in animals (Philibert., *et al*. 1982a, b). Two studies have also reported on its abortifacient properties in women. Complete abortion was reported in nine out of eleven subjects treated in one study (Herrmann., *et al*. 1982) and 22 out of 38 in the second (Kovacs., *et al*. 1984). Our laboratories recently commenced clinical trials with RU 486 in pregnant women in an attempt to induce abortion. The goal has been to evaluate the effect of various doses and duration of RU 486 treatment on the outcome" [17].

Given the long history of research on mifepristone it is understandable that the abortifacient equipotence of ulipristal acetate has become a focus of interest. Concerning this interest attention must be drawn to measures taken by the US FDA. The US FDA label for ulipristal as emergency contraception has included warnings since 2018 to assure that ulipristal acetate not be indicated for termination of existing pregnancies. "Attention should be drawn to the fact that some prescribing information, however, such as the US FDA label for ulipristal indicated for emergency contraception, has included new supplementary commentary since 2018 that directly warns about ulipristal not being indicated for termination of existing pregnancies and suggesting that ulipristal use may confer alterations to the endometrium that may affect implantation and contribute to efficacy" [5].

In view of the explicit warnings by the FDA since 2018, attention must be drawn to the legal regulations concerning abortion. Essential for these regulations is the emphasis on the physiological process of implantation. It is important to acknowledge that, from a legal perspective, it is implantation and not fertilization that is considered as the moment when pregnancy begins. "A judicial review in the UK in 2002 ruled that pregnancy begins at implantation and not fertilisation. This is an important consideration when discussing modes of action, particularly with emergency hormonal contraception (EHC), as some people may have their own beliefs about the onset of pregnancy and abortion" [18]. As is known from various US and international media, such as the Wallstreet Journal, legislation on abortion is intensively debated in the aftermath of the US Supreme Court ruling overturning Roe v. Wade. "Supreme Court Overturns Roe v. Wade, Eliminates Constitutional Right to Abortion" [19]. Most recently, legislation has been introduced to protect access to medication abortion based on the current "mifepristone Risk Evaluation and Mitigation Strategy (REMS)" [20]. This act is intended to defend access to medication abortion in those states where protection of the right to an abortion is still in existence, owing to the mifepristone Risk Evaluation and Mitigation Strategy. The act aims at enabling women to access abortion by means of telehealth and through certified pharmacies. "The Protecting Access to Medication Abortion Act would defend access to medication abortion in States where the right to an abortion is still protected by protecting the current mifepristone Risk Evaluation and Mitigation Strategy (REMS) so that women can always access medication abortion through telehealth and certified pharmacies, including mail-order pharmacies" [21].

In assessing the importance of REMS, it must be remembered that as early as 2003 a similar topic has been debated. In these debates, the FDA's restriction on the distribution of the drug has received particular attention and two issues have been criticized with respect to "physicians-only laws." The case in point was the FDA's restrictions, which limited the physicians' prescribing power by requesting special expertise as well as ability to provide surgical intervention care: "In approving mifepristone for use as an abortifacient, the FDA enumerated various restrictions on distribution of the drug. The drug must be provided by or under the supervision of a physician who is able to assess the duration of pregnancy accurately and to diagnose ectopic pregnancies. Practitioners prescribing mifepristone must either have the ability to provide surgical intervention in uncommon cases of incomplete abortion or severe bleeding, or have made plans to provide such

care through other qualified physicians. While complications are rare, providers must also be able to assure patient access to fully equipped medical facilities" [22]. In discussing the legal aspects of abortion it must be borne in mind that there is a concomitant area where abortion is a central issue, namely economics. Thus, a publication of 2021 investigated the microeconomics of abortion and drew attention to the problem of funding abortion-related costs by individuals. "The ways in which people pay for abortion-related costs are diverse. The intersection between micro-level costs and delay(s) to abortion-related care is substantial. Individuals forego other costs and expenditures, or are pushed further into debt and/or poverty, in order to fund abortion-related care. The evidence base on the economic impacts of policy or law change is from high-income countries, dominated by studies from the United States" [23].

As illustrated by the antecedent discussion, abortion is a multifaceted issue, addressed in numerous contexts, especially in the context of legislation and economics. Moreover, an abortifacient agent raises also ethical questions. As is generally known, in ethical debates not only the question of beginning of pregnancy but also the question of beginning of life is crucial.

Ethical aspects of ulipristal acetate as emergency contraceptive pill

In ethical discussion, efforts are made to clearly distinguish the process of implantation from the process of fertilization. Present-day legislation in most countries clearly defines implantation as the beginning of pregnancy. Ethical debates, on the other hand, bring the beginning of life into focus. Logically abortifacient medications play a pivotal role in discussions on the beginning of life, and the importance of ulipristal acetate as a potential abortifacient has been acknowledged not only in theoretical debates but also in pharmacological investigations. As illustrated in the description of the mechanism of action of ulipristal acetate, discussed above, its inclusion into the ethical debate is only logical. The finding that ulipristal acetate can educe post-fertilization effects "potentially raises alerts and/or ethical debates over the use of ulipristal owing to potential abortifacient activity" [5].

In fact, the ethical dimension of emergency contraception has been addressed as early as 2014 in medical contexts. In this publication-- a Review on Emergency Contraception -- the line of argument is twofold, namely first a comparison with other medications, and second a reference to the opinion voiced by several health agencies. In the first line of argument the authors draw attention to other emergency contraceptive pills (ECPs), including a natural method, namely breastfeeding, and affirm that these too might have post-fertilization effects. "To make an informed choice, women must know that ECPs—like the birth control pill, patch, ring, shot, and implant, and even like breastfeeding —prevent pregnancy primarily by delaying or inhibiting ovulation and inhibiting fertilization, but may at times inhibit implantation of a fertilized egg in the endometrium" [13]. Pursuing this line of argument, the authors go so far as to avouch that emergency contraceptive pills do not cause either harm to an established pregnancy or abortion: "ECPs do not cause abortion or harm an established pregnancy" [13]. Having asserted the safety of emergency contraceptive pills, the authors implement the second line of argument and refer to three health agencies. According to these agencies -- considered as "authorities" -- pregnancy begins with implantation and not with fertilization. "Pregnancy begins with implantation according to medical authorities such as the US FDA, the National Institutes of Health and the American College of Obstetricians and Gynecologists (ACOG)" [13].

In the face of this argumentation the question arises why the named agencies can be considered as "authorities" as none of them is a medical or biological research institute in the strict sense. Concerning the FDA, numerous criticisms must be borne in mind accusing this agency of failure to fulfill its role as the primordial agent of pharmacovigilance. Most recently, the FDA has been blamed for not acting on the complaints by women who experienced severe harm while using the copper-containing intrauterine device ParaGard. "The FDA received nearly 40,000 reports on Paragard in the FAERS (FDA Adverse Event Reporting System) database, with more than 15,600 involving serious complications such as ectopic pregnancy, broken IUDs, organ damage, and hysterectomies, and other surgeries to remove the IUD. They received over 7,000 reports of adverse effects in 2019 alone. The FDA has received reports of the deaths of approximately 15 women who used the ParaGard IUD" [24]. Already earlier, in 2018, criticism has been levelled against the FDA in conjunction with the Essure intratubal device for permanent contraception, which caused harm to thousands of women world-wide: "It's unbelievable that it took

the FDA since September to make just two recommendations with no enforcement measures and ask the manufacturer to perform another study while leaving Essure on the market" [24]. In addition to the criticism pertaining to contraceptive devices, the FDA has been criticized for its failure to provide complete and accurate information on birth control methods, especially with respect to its status as a public agency which is funded through taxpayer money [26]. The FDA's inferior orthographic competence should be mentioned only as a footnote by the following citation appearing in the context of the description of "some side effects" of levonorgestrel: "Headache, nausea, vomiting, dizzines /sic!/" [27]. Such inaptitude might be considered as a scandal only by champions of English orthography; but it reflects poorly on the FDA's attitude towards correctness and reliability.

As illustrated above, designating the FDA as an authority on contraception is ethically unjustifiable. Besides referring to arbitrarily chosen agencies which are misleadingly designated as "authorities," the argument advanced by the review of 2014 shifts the question of abortogenesis to the process of pregnancy by diverting attention away from the truly germane issue, namely the process of fertilization and beginning of life. It is precisely this issue that is addressed by an authority not mentioned by the review of 2014, namely the American College of Pediatricians. The statement made by this authority clarifies with scientific precision the central issue of the debate, namely the beginning of life. In 2017 appeared the statement entitled "When Human Life Begins" [28]. The abstract of this publication summarizes the results of human biological research and confirms unambiguously conception-fertilization as the beginning of life. "The predominance of human biological research confirms that human life begins at conception—fertilization. At fertilization, the human being emerges as a whole, genetically distinct, individuated zygotic living human organism, a member of the species Homo sapiens, needing only the proper environment in order to grow and develop. The difference between the individual in its adult stage and in its zygotic stage is one of form, not nature. This statement focuses on the scientific evidence of when an individual human life begins" [28]. It is important to note that this statement by the American College of Pediatricians highlights the question of the beginning of life as the key issue and not the beginning of pregnancy. If this distinction were acknowledged in ongoing debates, the arguments advanced would be more convincing and plausible.

Conclusions and Implications

The analysis of pharmacological aspects of ulipristal acetate as emergency contraceptive medication reveals that its potential abortifacient mechanism of action is still unresolved. The analysis of medical aspects brings to light the problem of determining the efficacy of ulipristal acetate as a contraceptive and shows the need for refining statistical methods. The analysis of the legal and ethical aspects of ulipristal acetate unveils the need for distinguishing between beginning of a pregnancy and beginning of life. On the basis of the findings of the critical analysis it can be suggested that future pharmacological research continue investigating abortifacient properties of contraceptives and their interactions with other drugs. Concerning medical findings statisticians should be encouraged to develop more sensitive tests and statistical methods suitable for assessing accurately the efficacy of emergency contraception and similar therapeutic options. Concerning legal and ethical deliberations, it can be recommended to pay heightened attention to scientific findings of medical and biological research and use them as the basis of arguments in lieu of opinions voiced by incompetent agencies or individuals.

Bibliography

1. Emergency Contraception. Practice Bulletin PB. Number 152. September 2015. ACOG (2022).

2. Brache V., *et al*. "Pharmacodynamics and pharmacokinetics of a copper intrauterine contraceptive system releasing ulipristal acetate: A randomized proof-of-concept study". *Contraception* 104.4 (2021): 327-336.

3. Mazza D. "Ulipristal acetate: An update for Australian GPs". *Australian Family Physician* 46.5 (2017).

4. Rosato E., *et al*. "Mechanism of Action of Ulipristal Acetate for Emergency Contraception: A Systematic Review". *Frontiers in Pharmacology* 6 (2015): 315.

5. PubChem. Ulipristal acetate | C30H37NO4 - PubChem (nih.gov) (2022).

6. ellaOne 30 mg tablet. "Ulipristal acetate. Package leaflet: Information for the user". ellaOne Package leaflet (hra-pharma.com) (2022).

7. DrugBank online. "Ulipristal: Uses, Interactions, Mechanism of Action" (2022).

8. Food and Drug and Drug Administration (FDA). "Birth Control Chart". FDA (2021).

9. Mikolajczyk RT and Stanford JB. "A new method for estimating the effectiveness of emergency contraception that accounts for variation in timing of ovulation and previous cycle length". *Fertility and Sterility* 83.6 (2005): 1764-1770.

10. Levy DP., *et al*. "Ulipristal acetate for emergency contraception: postmarketing experience after use by more than 1 million women". *Contraception* 89.5 (2014): 431-433.

11. Australian Prescriber. "Ulipristal acetate for emergency contraception" 6 (2022).

12. HWR Li., *et al*. "Efficacy of ulipristal acetate for emergency contraception and its effect on the subsequent bleeding pattern when administered before or after ovulation". *Human Reproduction* 31.6 (2016): 1200-1207.

13. Trussell J., *et al*. "Emergency contraception: a last chance to prevent unintended pregnancy" (PDF). Princeton: Office of Population Research at Princeton University, Association of Reproductive Health Professionals. Archived from the original (PDF) on September 23, (2010).

14. Keenan JA. "Ulipristal acetate: contraceptive or contragestive?" *Annals of Pharmacotherapy* 45.6 (2011): 813-815.

15. Food and Drug Administration (FDA). Mifeprix (Mifepristone) Information (2021).

16. Ware RS and Spitz IM. "Pharmacological properties of mifepristone: Toxicology and safety in animal and human studies". *Contraception* 68.6 (2003): 409-420.

17. Sitruk-Ware R., *et al*. "The Use of RU 486 as an Abortifacient in Early Pregnancy". In: Baulieu, EE., Segal, S.J. (eds) The Antiprogestin Steroid RU 486 and Human Fertility Control. Reproductive Biology. Springer, Boston, MA. (1985).

18. "Hormonal contraception: methods and patient eligibility". *The Pharmaceutical Journal* (2015).

19. The Wallstreet Journal. "Supreme Court Overturns Roe v. Wade, Eliminates Constitutional Right to Abortion". Supreme Court Overturns Roe v. Wade, Eliminates Constitutional Right to Abortion – WSJ (2022).

20. Advocacy and Health Policy. "Understanding the Practical Implications of the FDA's December 2021 Mifepristone REMS Decision". ACOG (2022).

21. U.S. Senator Tina Smith Introduces Legislation to Protect Access to Medication Abortions. Senator Tina Smith (senate.gov) (2022).

22. Center for Reproductive Rights. "Laws and Regulations Affecting Medical Abortion" (2003).

23. Coast E., *et al*. "The microeconomics of abortion: A scoping review and analysis of the economic consequences for abortion care-seekers". *PLoS One* 16.6 (2022): e0252005.

24. IUD Paragard Lawsuit: What the Course of Litigation in 2022 Depicts. Posted by Jerin Jose Nesamony (2022).

25. FORBES. "Did the FDA's actions on the Essure contraceptive go far enough?" (2022).

26. Kraetschmer KK. "The Need for Rectifying Heterodoxies and Flawed Science in Publications on Contraception and Birth Control". *Journal of Clinical and Laboratory Research* 5.3 (2022).

27. Food and Drug Administration. Birth Control Levonorgestrel. Some side effects (2021).

28. When Human Life Begins. American College of Pediatricians. March (2017).