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Research Article

Emergency Contraception: Ongoing Medical, Pharmacological, Political, and Ethical Controversies

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Abstract

The aim of the critical analysis is an illumination of unresolved issues on Emergency Contraception (EC). This form of contraception has been offered as an effective method of birth control to women since the end of the last century. At present -- in the post-Roe generation where access to abortion has been restricted -- the interest in EC is increasing. It is important therefore to provide accurate and complete information on which prospective users of EC can rely.

Material and Metho

The material encompasses documents issued by leading health authorities -- such as the World Health Organization (WHO), the US Food and Drug Administration (FDA), and the US Centers for Disease Control and Prevention (CDC) -- as well as research articles published in high-ranked scientific journals. This material is assessed by a critical analysis which compares the discrepancies in data provided and in claims made.

Results

The result is evidence of publications containing unreliable claims and conflicting views on some of the most salient aspects of EC such as safety, efficacy, mode of action, drug-drug interactions, legislation on abortion medication, and ethical discussions on the protection of life.

Implications

Consumers and patients should be critical towards claims made by health agencies and rather rely on high-level research in the area of pharmacovigilance and on publications by legal experts.

Keywords: abortion medication; safety; efficacy; mode of action; pharmacology; drug-drug interactions; abortion legislation; food and drug administration

1. Introduction

Over the past years, EC has been discussed extensively in various context, and it seems that these discussions have illuminated all pertinent aspects. The present critical analysis,however, argues that there are still unanswered questions and unsolved problems which are the object of numerous controversies. The most salient controversies appear in the areas of medicine, of pharmacology, of politics, and of ethics. The following analysis focuses on these areas and discusses controversies pertaining to medical issues, such assafety and efficacy, to pharmacological issues, such as mode of action and drug-drug interactions, on political issues, such as abortion medication and cost effectiveness, and on ethical issues, such as protection of life.

2. Medical controversies

Controversies in medicine revolve around three topics: safety, efficacy, and discontinuation of EC.

2.1-Safety

Concerning safety, attention must be drawn to a document on EC issued by the WHO in 2021 entitled "Emergency Contraception."[1] In this document, the WHO asserts in a nonspecific fashion that side effects are not common and are more or less negligible. "Side effects are not common, they are mild, and will normally resolve without further medications."[1] The claim that side effects are not common, mild, and without need for treatment cannot be confirmed by scientific research. In contrast to the WHO's claim, the manufacturer of ellaOne -- the most effective Emergency Contraceptive pill (ECP) containing Ulipristal Acetate (UPA) -- explicitly mentions common side effects: "Common side effects (may affect up to 1 in 10 people)

- nausea, abdominal (stomach) pain or discomfort, vomiting
- painful periods, pelvic pain, breast tenderness
- headache, dizziness, mood swings
- muscle pain, back pain, tiredness."[2]

Not only the manufacturer but also the FDA contradicts the WHO and mentions side effects which cannot be considered as mild or as transient. Indeed, for levonorgestrel the

FDA mentions menstrual changes, headache, nausea, vomiting, dizziness, lower stomach (abdominal) pain, breast pain, and tiredness. For ulipristal acetate the side effects considered as the "most common" by the FDA are: "Most Common Side Effects • Headache • Nausea • Abdominal pain • Menstrual pain • Tiredness • Dizziness"[3]

In the "Highlights of Prescribing Information" from 2015 the FDA provides even statistical data for the most common side effects. "The most common adverse reactions (≥ 10%) in the clinical trials for women receiving ella were headache (18% overall) and nausea (12% overall) and abdominal and upper abdominal pain (12% overall). Table 1 lists those adverse reactions that were reported in ≥ 5% of subjects in the clinical studies (14)."[4] Clearly, these statistical data cited in the Highlights of Prescribing Information and the list of "most common" side effects presented by the FDA in 2021 stand in sharp contrast to the WHO's claim that side effects are not common.

From an international perspective it is noteworthy that a German publication listed not only common but also frequent side effects such as: infection, psychic symptoms, headache, vertigo, nausea, vomiting, digestive symptoms, muscle spasm, back pain, menstrual pain, prolonged menstruation, and fatigue.[5]

Besides adverse events, the safety of the copper-bearing intrauterine device has to be considered as highly controversial. As is obvious from the WHO's document on EC from 2021, the claim is made that this device is not only the most effective but also a safe form of EC. "A copper-bearing IUD is a safe form of emergency contraception. "[1] The WHO's assertion that the copper-bearing device is a "safe form" of EC stands in sharp contrast to recent legal findings. Indeed, the copper-bearing intrauterine device"Paragard" is presently a topical issue in several courts of the US due to the severe injuries it has afflicted to thousands of women who were using it.[6]

Specifically mentioned side effects in legal proceedings include: "Anemia, Backache, Dysmenorrhea, Dyspareunia, Complete or partial expulsion, Prolonged menstrual flow, Menstrual cycle pattern changes, Menstrual spotting, Pain and cramping, Vaginitis."[6] US lawsuits claim that Paragard had a defective design as well as a manufacturing defect, that the label failed to warn, and that the manufacturer was negligent: "Paragard has a defective design because its design contributed to the tendency for its arms to break upon removal. • Paragard has a manufacturing defect that could have caused its arms to break. Paragard's label doesn't properly warn about the risks of breakage or tell doctors how to avoid breakage. Cooper Surgical and Teva Pharmaceuticals are negligent because they presented their devices as safe and effective but the devices caused harm to users."[7] In view of the numerous complaints and pending lawsuits concerning the safety of the copper bearing IUD, the question arises as to how the WHO can justify its statement that the copper IUD is a safe form of contraception.

Statement on safety play of course a pivotal role in in the clinical practice where women harbor two primordial questions: "Will it harm?" "and "Will it work?" The first question refers to adverse events, risks, and complications, and the second question refers to the efficacy of a given contraceptive method.

2.2-Efficacy

In attempts to describe the efficacy of EC, numerous controversial data have been presented. Thus the WHO claims that 95 % percent of pregnancies can be prevented: "Emergency contraception (EC) can prevent up to over 95% of pregnancies when taken within 5 days after intercourse."[1] To justify its claim, the WHO refers to a meta-analysis of two studies on UPA and levonorgestrel. "A meta-analysis of two studies showed that women who used ECPs with UPA had a pregnancy rate of 1.2%. Studies have shown that ECPs with LNG had a pregnancy rate of 1.2% to 2.1% (1) (2)."[1]

The two studies cited by the WHO are from the year 2011 and 2016 respectively. The first one focuses on the question as to whether it is possible to "identify women at risk of pregnancy despite using emergency contraception."[8] The second study focuses on the "Effect of BMI and body weight on pregnancy rates with LNG as emergency contraception."[9] Both publications appeared in the same journal, namely "Contraception," which has a Journal Impact Score (JIS) of 2.19. The data, which are uncritically replicated by the WHO do not harmonize with data presented by the FDA. In fact, the FDA claims for UPA: "In two large studies, 60 to 66% of expected pregnancies were prevented with correct use of ulipristal acetate."[3] For levonorgestrel, the FDA claims: "One large study showed 7 out of every 8 women who would have gotten pregnant did not become pregnant after taking emergency contraception; other studies have resulted in lower pregnancy prevention rates."[3]

The incongruities between the WHO data and the FDA data do not come as a surprise because as early as 2013 attention had been drawn to the problematicity of providing estimates for a preventive therapy. In fact, a highly influential review on EC drew attention to the problem of probability in measuring the effectiveness of a preventive therapy. "The effectiveness of a preventive therapy is best measured by comparing the probability that the condition will occur if the therapy is used to the probability that it will occur without treatment."[10, p.3] For calculating the effectiveness, the expected number of pregnancies and the observed number of pregnancies are used. "Effectiveness is calculated as 1-O/E, where O and E are the observed and expected number of pregnancies, respectively."[10, p.3]

For this calculation attention had been drawn to the difficulty of validating the numerous assumptions that have to be made. "Calculation of effectiveness, and particularly the denominator of the fraction, involves many assumptions that are difficult to validate.

Accurate estimates of efficacy depend upon accurate recording of timing of intercourse and cycle day (so that timing of ovulation can be estimated)."[10,p.3]

The difficulty of providing data on the efficacy of a preventive therapy is an ongoing issue. Thus, in 2016 a publication by Chinese authors provided information for determining the percentage of pregnancies prevented (PPP) and employed the following formula for calculating the main outcome measure, namely the PPP.

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

This study -- carried out in a community family planning clinic in Hong Kong -- presented data which emphasized the difference between pre-ovulatory and post-ovulatory status at the time of administration of UPA. "Main results and the role of chance: The PPP was significantly higher in subjects who were pre-ovulatory (77.6%) compared with those who were post-ovulatory (36.4%) at the time of UPA administration ($P < 0.0001$). The observed

pregnancy rate following UPA administration was significantly lower than the expected pregnancy rate only in the pre-ovulatory group ($P < 0.0001$), but not the post-ovulatory group ($P = 0.281$). The overall failure rate was 1.7% (1.4 versus 2.1% in the pre- and post- ovulatory groups, respectively)."[11] Despite the numerous data obtained in this study, the authors had to admit the limitations of their research pertaining to the ovulatory status. "Limitations, reasons for caution: The ovulatory status of the subjects was determined based only on menstrual history and a spot sonographic finding together with serum hormonal profile at the time of recruitment."[11]

2.3-Discontinuation of EC

Besides the problems of safety and efficacy, the clinical practice is faced with the question of discontinuing EC and resuming a different method of contraception. One of the most explicit recommendations to resume a regular method of contraception after ECP use emanates from the US Centers for Disease Control and Prevention (CDC). In fact, one of the primary concerns in the CDC's discussion of EC is the return from EC to a "regular hormonal" contraceptive method, and extended instructions are given for this transition.

Under the title "Initiation of Regular Contraception After ECPs" the CDC provides numerous recommendations for health care providers to manage the resumption of hormonal contraception after the use of UPA: "Advise the woman to start or resume hormonal contraception no sooner than 5 days after use of UPA, and provide or prescribe the regular contraceptive method as needed."[12]

In this context, the CDC draws attention to the risk for pregnancy in case of EC failure and the risk for unintended pregnancy if there is a delay in initiation of contraception. "The resumption or initiation of regular hormonal contraception after ECP use involves

consideration of the risk for pregnancy if ECPs fail and the risks for unintended pregnancy if contraception initiation is delayed until the subsequent menstrual cycle. A health care provider may provide or prescribe pills, the patch, or the ring for a woman to start no sooner than 5 days after use of UPA."[12]

As can be seen from this recommendation to resume a regular method, no mention is made about the particular life-style of an individual woman and the possibility of a reduced or declining sexual activity. Clearly, such a possibility should be taken into consideration according to principles of Precision Medicine. For women who engage in cohabitation no more than once a month there is no reason to abandon EC and switch to "regular" method. It is misleading therefore to recommend resuming a regular method to women who need to implement contraceptive measures no more than once a month.

In this context it should be noted that the same misleading information is disseminated by such renowned institutions as the Mayo Clinic which counsels that EC should not be used as a "routine" method of birth control. "Emergency contraception isn't meant to be used in place of routine birth control."[13] Obviously the same warning is propagated also by the FDA: "It should not be used as a regular form of birth control."[3] Logically, the recommendation to switch from EC to a regular form of contraception misleads millions of women with reduced or declining sexual activity who could safely continue using EC and therefore avoid the inconveniences of other methods such as daily administration of a pill or receiving a shot every three months.

From the perspective of public health, it seems unconceivable that such an important and well-described phenomenon as decline of sexual activity is neglected by leading health authorities. As early as 2008, the decline of sexual desires has been explored. "Sexual

desire declined with advancing age; overall, men reported more frequent and stronger sexual desire than women. However, there were important interactions between gender and age indicating an earlier decline among women."[14] The long-standing research on the decline of sexual desire and sexual activity stipulates a decreasing need for contraceptive measures so that UPA once per menstrual cycle would provide sufficient protection and greatly enhance a woman's quality of life. Moreover, financial benefits through avoiding costly contraceptive methods, such as implants, might be an important issue for some segments of the population.

Concerning the discontinuation of EC, attention should be drawn also to findings about the pharmacodynamics of UPA. As early as 2013 it was reported that a study on pharmacodynamics did not demonstrate any safety concerns in cases of repeated use of UPA for EC. "However, a pharmacodynamic study of repeated use of UPA EC (every 7 days for 8 weeks) showed no safety concerns, indicating that UPA can be safely used more than once per cycle. The same study found that the majority of women in a smaller subgroup ovulated at least once during this period, suggesting that this may not be an effective longer-term method. In addition, recent comprehensive review by CDC/WHO did not suggest any special safety concerns for the use of any type of ECPs among women with particular medical conditions or personal characteristics, such as pregnancy, lactation or frequent ECP use."[10, p.8] The two studies quoted in this citation investigated the safety of repeated use of 30 mg UPA [15], on the one hand, and the safety of the UPA, levonorgestrel, and the Yuzpe regimens, on the other.[16] These insights into the possibility of repeated use of UPA give additional support to the argument of using EC without resuming a regular method of contraception, as is recommended by such leading health authorities as the FDA, the CDC and the Mayo Clinic.

2.4-Completeness of information on EC

Besides controversies on efficacy, safety, and discontinuation of EC the issue of completeness of information deserves attention. Neither the WHO, which asserts to provide guidance, nor the FDA, which claims to provide "high-level information about different 'birth control' options,"[3] nor the CDC mention the most recently described method for EC, namely the copper intrauterine contraceptive system releasing UPA.

The neglect of this method of contraception is the more deplorable as it offers desirable advantages according to a proof-of-concept study. Indeed, this study of 2021 identified advantages such as reduction of bleeding and absence of serious adverse events. "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."[17] Although the statement that adverse events are absent seems to be premature, the existence of this method should have been acknowledged not only by the WHO but also by the FDA and the CDC.

3- Controversies in pharmacology

Controversies in pharmacology pertain to four topics, namely mode of action, effects of mifepristone, drug-drug interaction, and repeated use of UPA as EC.

3.1-Mode of action

Concerning the issue of mechanism of action, attention has been drawn to conflicting standpoints in the literature. Earlier research studies seemed 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 has been challenged by more recent investigations which draw attention to a post-fertilization effect of UPA (cf. Figure 1).

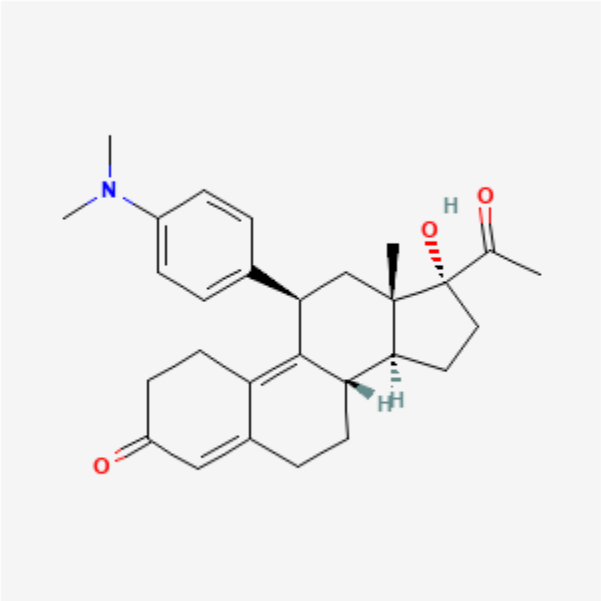

Figure 1: Chemical Structure Depiction of UPA [18]

Concerning pharmacodynamics of UPA, attention has been drawn to the difference between administration in mid-follicular phase, administration at the luteinizing hormone peak, and administration during early luteal phase. ”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.”[19]

In the description of the mode of action, embryo-implantation has been underlined as the result of current and ongoing research. The primary evidence seems to come from endometrial biopsy samples which show the down-regulation of certain genes considered essential for a receptive pro-gestational endometrium. “Endometrial biopsy samples studied from such circumstances in such investigations subsequently show that the administered ulipristal causes endometrial tissue to become inhospitable and unsuitable for embryo implantation where a variety of genes characteristic of receptive, pro- gestational endometrium are downregulated 10,11,12.”[19] The most important claim concerns the equipotence with mifepristone, the widely-used abortion medication. “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 9,10,11,12, which is considered to be on par or equipotent to that of mifepristone.”[19]

Concerning the statement that the abortifacient potential of UPA is commensurate with that of mifepristone, earlier research has to be borne in mind. As early as 2011 a publication drew attention to 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.”[20].

The claim that UPA could be used as an effective abortifacient and its structural similarity with mifepristone logically raise the question of abortion medication, which has been playing a prominent role for quite some time in pharmacological research. Figure 2 shows the structure of mifepristone.

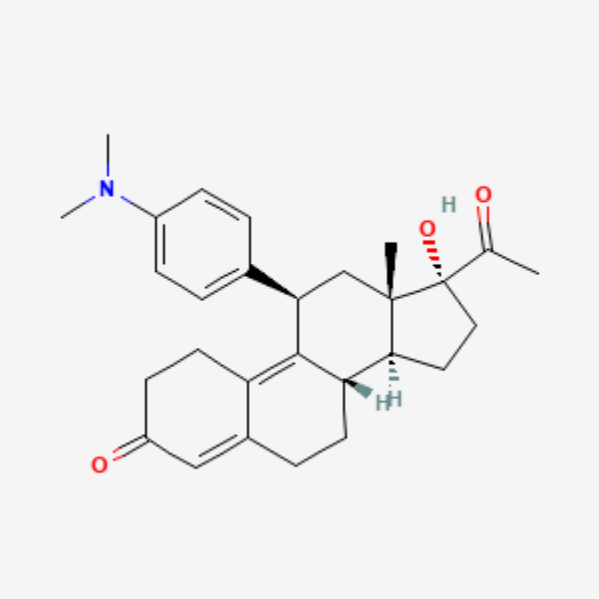

Figure 2: Chemical structure depiction of Mifepristone.[21]

3.2-Effects of Mifepristone

Pharmacological research on mifepristone as a medication for termination of pregnancy (TOP) or induced abortion has a long history. As early as 2003 the pharmacological properties of mifepristone have been described, including its suitability for termination of early pregnancy. "Its use was extended to other indications, such as cervical dilatation prior to surgical TOP in the first trimester, therapeutic TOP for medical reasons beyond the first trimester, and for labor induction in case of fetal death in utero."[22]

Concerning the findings of this publication from the year 2003, it must be borne in mind that it is based on earlier research. More distinctly, in 1985 an influential publication discussed the abortifacient properties of RU 486 in early pregnancy by referring to still earlier studies of 1982 and 1984. "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."[23]

In light of the extensive and extended research on mifepristone it is not surprising that the US FDA has issued a number of documents related to this abortion medication within the so-called Risk Evaluation and Mitigation Strategies (REMS) program. In a document current as of 2023 the FDA specified:

"Under the Mifepristone REMS Program:

- Mifepristone must be prescribed by a health care provider that meets certainqualifications and is certified under the Mifepristone REMS Program.
- In order to become certified to prescribe mifepristone, health care providers mustcomplete a Prescriber Agreement Form.
- The Patient Agreement Form must be reviewed with and signed by the patient andthe health care provider, and the risks of the mifepristone treatment regimen must be fully explained to the patient before mifepristone is prescribed.
- The patient must be provided with a copy of the Patient Agreement Form and mifepristone Medication Guide (FDA-approved information for patients).
- Mifepristone may only be dispensed by or under the supervision of a certifiedprescriber, or by a certified pharmacy on a prescription issued by a certified prescriber.
- To become certified to dispense mifepristone, pharmacies must complete a Pharmacy Agreement Form.
- Certified pharmacies must be able to ship mifepristone using a shipping service that provides tracking information.
- Certified pharmacies must ensure mifepristone is dispensed to the patient in atimely manner."[24]

In the same year, the FDA reported serious adverse events, including fatal outcomes. "The FDA has received reports of serious adverse events in patients who took mifepristone. As of June 30, 2022, there were 28 reports of deaths in patients associated with mifepristone since the product was approved in September 2000, including two cases of ectopic pregnancy (a pregnancy located outside the womb, such as in the fallopian tubes) resulting in death; and several fatal cases of severe systemic infection (also called sepsis)."[25]

In a document of 2021, the FDA specified the REMS program in general,[26] and in 2022 the FDA described the REMS Compliance

Program containing the warning: "Failure to comply with REMS requirements may result in enforcement action such as product seizure, injunction or civil money penalties."[27]

3.3-Drug-drug interactions

Concerning the topic of drug interactions the FDA presented extensive data, especially on the effect of other drugs on UPA and the effect of UPA on other drugs. Thus, in 2010 the "Office of Clinical Pharmacology Review" drew attention to the role of CYP3A4 in the metabolism of UPA: "Effects of other drugs on ulipristal acetate. In vitro data indicate that the metabolism of ulipristal acetate is predominantly mediated by CYP3A4 (See section 2.2.3.3.) Concomitant administration of CYP3A4 inhibitors may inhibit the metabolism of ulipristal acetate and cause increased plasma concentration of ulipristal acetate."[28, p.32] What is important to note regarding the "Office of Clinical Pharmacology Review" is the assertion that no safety concerns were identified in the phase 3 studies. "However, there was no safety concern identified in the phase 3 studies (HRA2914-509 and HRA2914-

513). In addition, concomitant administration of CYP3A4 inducers may reduce plasma concentrations of ulipristal acetate and may result in decrease in efficacy."[28, p.32] Given uncertainties with CYP3A4 inducers, the FDA requested as a post-marketing requirement the performance of in vivo drug-drug interactions with CYP3A4 inducer. "Therefore, in vivo drug-drug interaction trial with CYP3A4 inducer needs to be conducted as post marketing requirements."[28, p.32]

Concerning the effect of UPA on other drugs the FDA emphasized the findings of three in- vitro studies: "The effect of ulipristal acetate on other drugs - Based on the findings from three in vitro studies (HRA2914-430, HRA2914-476, and

HRA2914-477), it is unlikely that the CYP inhibition and CYP induction (CYP1A2 and CYP3A4) by ulipristal acetate and 3877A detected in vitro had clinical relevance."[28, p.32] Surprisingly, the FDA found the results of the studies performed as sufficient and considered it redundant to further investigate inhibition or induction of CYP enzyme activity by UPA. "Therefore, no further in vivo studies to evaluate inhibition or induction of CYP enzyme activity by ulipristal acetate or 3877A are warranted."[28, p.32]

From a historical viewpoint it is worth noting that the FDA admitted the lack of studies on specific drug or food interactions with mifepristone in its publication of 2000. "Drug Interactions - Although specific drug or food interactions with mifepristone have not been studied, on the basis of this drug's metabolism by CYP 3A4, it is possible that ketoconazole, itraconazole, erythromycin, and grapefruit juice may inhibit its metabolism (increasing serum levels of mifepristone). Furthermore, rifampin, dexamethasone, St.

John's Wort, and certain anticonvulsants (phenytoin, phenobarbital, carbamazepine) may induce mifepristone metabolism (lowering serum levels of mifepristone)."[29] Concerning in vitro inhibition, it had been assumed that the coadministration of mifepristone may lead to an increase in serum levels of drugs that are CYP 3A4 substrates. Given the slow elimination of mifepristone from the body, this kind of interaction may persist over a longer period of time subsequent to administration. As a consequence, the FDA recommended caution. "Therefore, caution should be exercised when mifepristone is administered with drugs that are CYP 3A4 substrates and have narrow therapeutic range, including some agents used during general anesthesia."[29]

Besides the FDA's statements on drug interactions the claims made by the manufacturer deserve attention. Under the heading "Other medicines and ellaOne" the manufacturer's leaflet draws attention to five medications, namely those for epilepsy (primidone, phenobarbital, phenytoin, fosphenytoine, carbamazepine, oxcarbazepine and barbiturates); those for tuberculosis (rifampicin, rifabutin); those for HIV (ritonavir, efavirenz, nevirapine); those for fungal infections (griseofulvin), and to herbal remedies containing John's wort (Hypericum perforatum).[2]

In contrast to the five medications relevant for interactions with ellaOne, according to the manufacturer, ten drugs are enumerated in a drugbank of 2023, namely Abametapir, Abciximab, Acenocoumarol, Acetaminophen, Acetazolamide, Acetohexamide, Alpelisib, Alteblase, Aminogluthetimide, and Amiodaron.[19] Interactions of UPA have also been the object of biomolecular studies which investigated interactions between ulipristal acetate (UPA) and human serum albumin (HSA) "in simulated physiological environment using multi-spectroscopic and computational methods."[30] Regrettably, the manufacturer of ellaOne does not mention any of the interactions investigated by various studies but limits its enumeration to the five indications (epilepsy, tuberculosis, HIV, fungal infection, andherbal products) mentioned above.[2]

What should be noted with respect to the limited number of drug-drug interactions mentioned by the manufacturer of ellaOne, is the paucity of studies devoted specifically to UPA: Thus, a publication of 2021 could identify only three relevant studies and shed light on the role of CYP3A4 inducers in drug-drug interactions (DDI) by using the "in vivo mechanistic static model" (IMSM) approach. "For UPA, only three studies were identified, including only one CYP3A4 inducer. The IMSM approach indicated that UPA is a sensitive substrate of CYP3A4, with an estimated contribution of 86% of CYP3A4 to oral clearance. Moderate to severe DDI were predicted in 17 cases with CYP3A4 inducers, and dosage adjustments were suggested. This study illustrates the ability of the IMSM approach to inform about the DDI profile of old and new drugs."[31]

What must be borne in mind concerning the prediction of the magnitude of drug-drug interaction in general is the existence of two approaches, the in vivo mechanistic static model (IMSM) on the one hand, and the physiologically-based pharmacokinetic model (PBPK) on the other: "The in vivo mechanistic static model (IMSM) and the physiologically based pharmacokinetic (PBPK) model are two approaches used to predict the magnitude of drug–drug interactions (DDIs)."[32] As mentioned above, the IMSM approach could show that UPA is a sensitive substrate of CYP3A4.

3.4-Pharmacodynamic studies on repeated use of UPA as EC

Besides mode of action and drug interaction the repeated use of UPA for EC is a matter of controversy. De facto, a pharmacodynamic study of 2016, mentioned above,[10] asserted the safety of repeated use of UPA and underlined its potential for preventing an unintended pregnancy in case of further unprotected intercourse. "Conclusions: Repeat use of 30 mg oral UPA every 5 or 7 days for 8 weeks initially delays follicular rupture but ovulation eventually occurs with time in most subjects. Safety data indicate that UPA 30 mg could be safely administered if needed more than once for EC in a given menstrual cycle."[33]

As implications of their findings the authors confirm the safety of repeated use of UPA 30 mg and underline its effectiveness also for future incidences of unprotected intercourse. "Implications: These data demonstrate that repeated use of UPA 30 mg is safe. However, ovulation eventually occurs in a high proportion of women in spite of repeated treatments in both studied regimens. Nevertheless, since the stage of follicular development of women seeking initial or repeat EC use is generally unknown, the repeated use of UPA may still delay follicular rupture and prevent an unintended pregnancy in the event of further unprotected intercourse."[33] Unfortunately, this finding concerning the

safety of repeated use of UPA has not yet been incorporated into the clinical practice where women are still advised to resume a regular method of contraception subsequent to the administration of UPA as EC."[12]

4-Political controversies on medications for abortion

ECPs are relevant for political discussions as they have abortifacient potentials, and abortion is a controversial issue in the post-Roe generation of the USA. As political discussions are guided by economic consideration, the problem of cost-effectiveness must also be addressed.

4.1-Politics and legislation

Controversies in politics and legislation presently focus on abortion medications and its accessibility through telehealth and certified pharmacies, including mail-order pharmacies. One of the most recent attempts to safeguard access to abortion medication has been undertaken to protect the access to medication abortion in certain states of the USA. "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."[34] As can be seen the aim of this act is codification of the current mifepristone REMS program, mentioned above.[24-27] This means that the act does not postulate a new regulation but the codification of the already existing REMS program. "This legislation would protect access to medication abortion pills by codifying the current mifepristone Risk Evaluation and Mitigation Strategy (REMS) to make sure that those looking to access reproductive healthcare can continue to do so."[35] The importance of this kind of medication is emphasized by drawing attention to the advantages of the long- standing REMS program. "Medication abortion accounts for over half of all abortion care performed in the United States and remains effective for the first ten weeks of gestation.

The regime has been FDA approved for over two decades, can be prescribed without an in-person appointment, and can be safely administered at home."[35]

4.2- Cost-effectiveness

Warranting access to abortion medication through telehealth, certified pharmacies, and mail order pharmacies, involves financial burdens for the health system so that cost- effectiveness is a central issue in political discussions on abortion. For this issue numerous data have been provided, but the model on which they are based is of hypothetical nature so that the estimates proposed are highly speculative. A study of 2018 estimated the medical costs and unintended pregnancies over one year and found that the copper intrauterine device was the most effective in comparison with UPA, with levonorgestrel, and with a combination of oral levonorgestrel plus intrauterine device containing levonorgestrel (Mirena). The results of the model applied were estimates for medical costs for 1000 women requesting EC. "Results: In 1000 women seeking emergency contraception, the model estimated direct medical costs of $1,228,000 and 137 unintended pregnancies with ulipristal acetate, compared to $1,279,000 and 150 unintended pregnancies with oral levonorgestrel, $1,376,000 and 61 unintended pregnancies with copper intrauterine devices, and $1,558,000 and 63 unintended pregnancies with oral levonorgestrel plus same-day levonorgestrel intrauterine device."[36] The copper intrauterine device proved to be the most cost-effective option for EC in most of the model iterations and in comparison with UPA. "The copper intrauterine device was the most cost-effective emergency contraception strategy in the majority (63.9%) of model iterations and, compared to ulipristal acetate, cost $1957 per additional pregnancy prevented."[36]

The conclusion drawn in this publication makes recommendations relevant for both policy makers and health insurance companies. Both are advised to consider the potential for long-term savings and prompt access to intrauterine devices. "Conclusion: Over 1 year, the copper intrauterine device is currently the most cost-effective emergency contraception option. Policy makers and health care insurance companies should consider the potential for long-term savings when women seeking emergency contraception can promptly obtain whatever contraceptive best meets their personal preferences and needs; this will require removing barriers and promoting access to intrauterine devices at emergency contraception visits."[36]

As can be seen from the emphasis on the cost-effectiveness of the copper intrauterine device, whose safety is being questioned by ongoing lawsuits in the US, the study fails to take into consideration aspects of safety and quality of life. Above all, it is limited to the use of only one year, and the clinical practice typically has to respond to the needs for longer periods of EC use. From a clinical viewpoint one might also argue that a study on cost- effectiveness should not be indifferent to the question of prevention of EC through intensified information on the numerous forms of contraception presently available.[37]

5- Ethical Controversies

Ethical controversies revolve primarily around two issues, namely the abortifacient potential of ECPs and the consequences of the Supreme Court's decision overturning Roe

v. Wade for the post-Roe generation.

5.1-Ethical discussions on the abortifacient potential of ECPs

Ethical question pertaining to medication abortion pills have a long history. Thus, at the time of the introduction of RU486 into the USA the question was asked: "Does the prospect of introducing RU 486 into the United States pose any unique ethical issues or are the ethical questions raised by antiprogestins similar to those that arise when any new medical technology comes along."[38]

More recently, in 2013, the ethical issue has been addressed in a review on EC mentioned above.[10] Under the heading "Mechanism of action" the authors discussed the abortifacient potential of ECPs, and their fundamental assertion was that ECPs do not interrupt an established pregnancy. To prove the validity of their claim the authors made reference to some institutions which they considered as "medical authorities." "ECPs do not interrupt an established pregnancy, defined by medical authorities such as the United States Food and Drug Administration/National Institutes of Health and the American College of Obstetricians and Gynecologists as beginning with implantation. Theref ore, ECPs are not abortifacient."

As can be seen from this argument, pregnancy is considered as beginning with implantation. In the face of such a consideration the question arises why the process of fertilization remains unmentioned. Indeed, according to biological sciences, it is the moment of fertilization and not the process of implantation that should be considered as the beginning of pregnancy. "Human development begins after the union of male and female gametes or germ cells during a process known as fertilization (conception).

Fertilization is a sequence of events that begins with the contact of a sperm (spermatozoon) with a secondary oocyte (ovum) and ends with the fusion of their pronuclei (the haploid nuclei of the sperm and ovum) and the mingling of their chromosomes to form a new cell. This fertilized

ovum, known as a zygote, is a large diploid cell that is the beginning, or primordium, of a human being."[39]

As can be seen, biological sciences consider the process of fertilization as the beginning of gravidity. It is therefore an entirely arbitrary decision if some institutions define implantation as the beginning of pregnancy. Moreover, it is inaccurate to speak nonspecifically of implantation without taking into consideration that implantation or nidation is a process that lasts several days, from the 6th day to the 10th day subsequent to fertilization. Scientifically it is incorrect, therefore, to neglect the duration of this process and speak vaguely of implantation as if it were a punctual event. The relevance of scientific precision can be seen from German legislation which specified the completion of implantation as germane for laws on abortion. Thus, German penal law § 218, specifies that use of nidation inhibitors, which exert their effect prior to nidation, are not considered criminal offence. [40, p.1168]

It should be noted that the concept of implantation as a process of several days is critical not only in bioethics but also in forensic medicine which is faced with the problem of determining the beginning of pregnancy. For paternity suits, the difficulty of calculating the period of gestation has been discussed as early as 1972. “The period of gestation, irrespective of the assertions of the parties in a certain case, is unable to clarify the biologic process to the extent required legally. The probabilities which are ascertained can only assist in arriving at a conclusion and do not have the value of the serological or anthropological determinations.”[41]

The fundamental concept for paternity suits is the period of gestation, and the forensic literature considers conception, that means fertilization, as essential for determining the duration of pregnancy. For this determination, two methods are commonly used, namely post conceptionem and post menstruationem.[40, p.1517] The first calculates 263 to 273 days from the day of conception -- and not implantation -- and the second calculates approximately 280 days from the first day of menstruation of the last period.

The claim that pregnancy begins with implantation, as described by the authors in the review from 2013, can therefore not be validated on grounds of both forensic medicine and biological sciences. In addition to abandoning scientific grounds in their definition of pregnancy, the authors also fail to provide convincing ethical arguments by their reference to arbitrarily chosen “medical authorities.” None of the cited “authorities” is a genuine research institution qualified to comment on the complex biological processes of fertilization and nidation.

A further weakness of the argument advanced in the publication of 2013 is the attempt to compare methods of contraception despite diverging probabilities of mode of action. “To make an informed choice, women must know that ECPs—like all regular hormonal contraceptives such as the birth control pill, the implant Implanon, the vaginal ring NuvaRing, the Evra patch, and the injectable Depo-Provera,98 and even breastfeeding99- 102—prevent pregnancy primarily by delaying or inhibiting ovulation and inhibiting fertilization, but it is not scientifically possible to definitively rule out that any of these methods, including breastfeeding, may inhibit implantation of a fertilized egg in the endometrium.”[10, p.8]

This argument can hardly be justified on ethical grounds because it seems ethically questionable to compare the high probability of a post-fertilization event caused by UPA to the extremely low probability of such an event caused by other methods including breast feeding. Among the weaknesses of the arguments advanced by the authors, the reference to arbitrarily chosen “authorities” seems to be one of the most problematic. More to the point, it must be asked why other authorities, such as the American College of Pediatricians (ACPs) have been neglected.

5.2-The ethical discussions on abortion

As is known, the ACPs provided an extensive discussion on the biological processes of fertilization and embryonic development relevant for questions pertaining to pregnancy. Based on this discussion they commented on the Supreme Court’s decision by emphasizing the importance of a “life ethics.” “The Supreme Court is finally upholding the dignity of human life, and this is long overdue. The integrity of the medical profession depends upon a consistent life ethic. Now our nation can continue to disentangle the life- giving mission of the medical profession from the deadly practice of abortion The practice of pediatrics will benefit immeasurably from this life-affirming decision in Dobbs v. Jackson and the overturning of Roe v. Wade.”[38]

Diametrically opposed to this statement by the ACPs, underlining the life-giving mission of the medical profession, is the comment made by another US medical organization, the College of Obstetricians and Gynecologists (ACOG).

The ACOG argues on the grounds of “bodily autonomy,” that access to medical care will no longer be possible for a large number of women. “Today's decision is a direct blow to bodily autonomy, reproductive health, patient safety, and health equity in the United States. Reversing the constitutional protection for safe, legal abortion established by the Supreme Court nearly 50 years ago exposes pregnant people to arbitrary state-based restrictions, regulations, and bans that will leave many people unable to access needed medical care.”[42] What is particularly noteworthy in this comment by the ACOG is the argument that the restrictions generated by the Supreme Court’s decision are not based on science or medicine and constitute a denial of bodily autonomy. ”The restrictions put forth are not based on science or medicine; they allow unrelated third parties to make decisions that rightfully and ethically should be made only by individuals and their physicians. ACOG condemns this devastating decision, which will allow state governments to prevent women from living with autonomy over their bodies and their decisions.”[43]

In considering these opposing viewpoints not only from an ethical perspective but also from the economic viewpoint of profit maximization, it is clear that the possibility to perform abortions provides financial gains for gynecologists. On the other hand, increased numbers of childbirths enhance profits for pediatricians.,

6-Conclusions and Implications

In conclusion, special attention should be drawn to some of the most salient findings of this critical analysis, namely the medical controversies concerning the discontinuation of EC, the pharmacological controversies, revolving around UPA as an abortion pill, the political controversies dwelling on access to abortion medication, and the ethical discussions preoccupied with the beginning of pregnancy versus beginning of life.

Implications

Future medical controversies on the repeated use of EC can be clarified by taking into account research on the decline of sexual activity. Pharmacological controversies will benefit from acknowledging the results of past studies on the potentials of UPA. Political controversies should be based on scientific evidence and not on personal beliefs or superstition. Ethical controversies should acknowledge the result of biological research and refrain from relying on arbitrarily chosen and unqualified authorities.

Conflict of Interest

The author declares the absence of any conflicting interests

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