Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 7 Issue 5 May 2023

Research Article

A Critical Analysis of Information Presented by the World Health Organization on Emergency Contraception

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Received: March 13, 2023

Published: April 12, 2023

Abstract

Aim: On the background of limited access to abortion and ensuing increased interest in Emergency Contraception (EC) in post-Roe USA, the aim of the present critical analysis is to answer the question as to whether women can rely on information presented by the World Health Organization (WHO) pertaining to Emergency Contraception.

Method: The material used are documents issued by the WHO and other health agencies as well as high-ranked research publications. This material is analyzed by using a critical analytic method which assesses the accuracy of claims made and the validity of the data presented by a comparative method.

Result: The result of the critical analysis is evidence that the information by the WHO is not trustworthy and that millions of women worldwide are misled on such issues as mode of action, efficacy, and safety of EC. The WHO's information on the mode of action denies explicitly post-fertilization effects of EC despite results of evidence-based pharmacological research and statements made by the European Medical Agencies (EMA). The WHO's data regarding efficacy of EC are incompatible with data presented by the FDA. The WHO's explanations on safety belittles adverse events and ignores the harm caused by the copper-bearing intrauterine device which is presently the object of ongoing lawsuits in the USA. Regarding options for EC, the WHO disseminates incomplete information by ignoring the copper intrauterine contraceptive system releasing ulipristal acetate.

Implication: As implication of the misleading information provided by the WHO the question arises whether the WHO can be considered as an agency that provides guidance and accomplishes its mission as a foremost agent of pharmacovigilance. Given that women cannot trust information contained in various publication by the WHO, governments and private donors should revise their policies of financial support for the WHO.

Keywords: Contraception; World Health Organization; Food and Drug Administration; Drug Safety, Drug Efficacy; Drug-Drug Interactions; Paragard Lawsuits

Introduction

Given the WHO's prominent role as an international health authority it is logical that women world-wide consult documents issued by the WHO and trust that they can rely on them. This confidence is corroborated by the fact that the WHO published a document specifically devoted to EC. In this document from 2021 the WHO asserts its commitment to continuously assessing "emerging evidence" through its own system, the "Continuous Identification of Research Evidence" system and to updating its "guidance" function: "WHO reaffirms its commitment to constantly reviewing emerging evidence through its Continuous Identification of Research Evidence (CIRE) system and also by regularly updating its guidance accordingly" [1].

As can be seen from this statement, permanently reviewing surfacing evidence and providing adequate guidance are the WHO's primary targets. In view of this proposal, it can be expected that the documents on EC issued by the WHO contain accurate and reliable information on the salient aspects of EC, such as mode of action, safety, efficacy, and completeness of information. The following discussion focuses on these aspects by presenting the relevant statements contained in the WHO's documents devoted to EC and by critically analyzing them according to principles of evidence-based medicine.

WHO's statements on mode of action, safety, and efficacy of EC

Concerning efficacy, the WHO states that more than 95% of pregnancies can be prevented through EC. "Emergency contraception (EC) can prevent up to over 95% of pregnancies when taken within 5 days after intercourse" [1]. Among the situations where EC can be used the WHO lists unprotected intercourse, assumptions of contraceptive failure, incorrect use of a contraceptive method, and "sexual assault if without contraception coverage" [1]. As regards forcible intercourse, it should be noted that the US Centers for Disease Control and Prevention (CDC) limits the implementation of EC to those cases where a pregnancy can be surmised. "Emergency contraception should be considered when the assault could result in pregnancy (see Emergency Contraception)" [2].

As methods for EC the WHO enumerates the copper-bearing intrauterine device as well as emergency contraceptive pills (ECPs) and considers the first as the most effective form of EC. "A copper-bearing IUD is the most effective form of emergency contraception available" [1]. Regarding the pills for, the WHO specifies: "ulipristal acetate, levonorgestrel, or combined oral contraceptives (COCs) consisting of ethinyl estradiol plus levonorgestrel" [1].

Pertaining to the topic of mechanism of action, the WHO addresses the controversial issue of abortion and insists on the absence of any abortive effect of EC pills by stating: "Mode of action - Emergency contraceptive pills prevent pregnancy by preventing or delaying ovulation and they do not induce an abortion. The copper-bearing IUD prevents fertilization by causing a chemical change in sperm and egg before they meet. Emergency contraception cannot interrupt an established pregnancy or harm a developing embryo" [1].

With respect to the safety of pills for EC, the WHO explains that side effects are similar to those of oral contraceptive pills and characterizes them as rare, mild and without need for treatment: "Safety - Side effects from the use of ECPs are similar to those of oral contraceptive pills, such as nausea and vomiting, slight irregular vaginal bleeding, and fatigue. Side effects are not common, they are mild, and will normally resolve without further medications" [1]. Despite the assertion that side effects are only "mild" and transient, the WHO provides extensive information on vomiting, one of the most common adverse events in EC. "If vomiting occurs within 2 hours of taking a dose, the dose should be repeated. ECPs with LNG or with UPA are preferable to COCs because they cause less nausea and vomiting. Routine use of anti-emetics before taking ECPs is not recommended" [1]. Regarding consequences for future fertility, the WHO negates any such sequelae. "Drugs used for emergency contraception do not harm future fertility. There is no delay in the return to fertility after taking ECPs" [1].

What should be noted in the WHO's explanations on safety are the comments on the copper-bearing IUD and the emphasis on pelvic inflammatory disease (PID). "Safety - A copper-bearing IUD is a safe form of emergency contraception. It is estimated that there may be less than 2 cases of Pelvic Inflammatory Disease (PID) per 1000 users (3). (FP Global Handbook). The risks of expulsion or perforation are low" [1].

Critical appraisal of the assertions made by the WHO on EC

Mode of action

As regards the mode of action of EC pills, the WHO states that they prevent or delay ovulation and explicitly denies the possibility of post-fertilization effect by claiming: "they do not induce an abortion" [1]. This denial of an abortifacient potential is all the more surprising as other health agencies and research publications express different opinions. Thus, the US FDA assumes for ulipristal acetate (UPA) not only inhibition or delay of ovulation, but also a post-fertilization effect, due to changes in the endometrium. More specifically, for ulipristal acetate, the FDA describes the mode of action by drawing attention to changes in the "lining of the womb," which means alterations in 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)" [3]. As can be seen, the post-

fertilization effects of UPA, which are explicitly mentioned by the FDA, are denied in an unequivocal manner by the WHO: "they do not induce an abortion" [1].

The WHO's denial of any abortifacient potentials not only contradicts the FDA's statement but also pharmacological research. This research has repeatedly emphasized the similarity between UPA and Mifepristone, the widely recognized abortion pill, known also as RU 486 or morning-after pill. Given this similarity, as early as 2011, the question has been raised as to whether UPA should be considered a "contragestive" and not only a "contraceptive" [4]. Figure 1 shows the structural formula of UPA [5].

Figure 1: Ulipristal Acetate [5].

From an international perspective it is worth noting that as early as 2019, ie, two years previously to the publication of the WHO's document on EC, a research publication explicitly insisted on the prevention of embryo implantation by referring not only to statements made by the European Medicines Agency (EMA) but also by citing ongoing research. "Lastly, Lira-Albarran administered ellaOne((R)) to women in the most fertile pre-ovulatory days: they had normal ovulation, but their endometrium, evaluated through samples obtained in the implantation window, became inhospitable: the expression of 1183 genes was exactly the opposite of that observed in the receptive pro-gestational endometrium. This agrees with information by EMA-CHMP-Assessment Report 'EMEA/261787/2009' (p. 8): after UPA administration 'the proteins necessary to begin and maintain pregnancy are not synthesized" [6]. The conclusion drawn in this publication leaves no doubt about the abortifacient potential of Emergency Contraceptives: "CONCLUSIONS: Emergency Contraceptives work prevalently by preventing embryo-implantation. People shall receive correct information" [6].

A more recent study of 2021 investigated gene expression profile in endometrial cells. The authors of this study assumed a down-regulation of genes involved in preparing the endometrium for implantation. "Conclusions - When UPA was administered after ovulation, it seems to induce a down-regulation of the main genes involved in conditioning the endometrium for implantation" [7].

By denying any implantation effect of EC pills, the WHO ignores not only recent research in reproductive health but also pharmacological research dating back to the year 2011 [4]. In doing so, the WHO contradicts both the FDA's statement on endometrial changes caused by UPA and the EMA's declaration on anti-implantation effects of UPA.

Safety

Some of the most misleading claims made by the WHO are those pertaining to the safety of EC. More specifically, the WHO claims that side effects are only mild, rare, transient and without need for treatment: "Side effects are not common, they are mild, and will normally resolve without further medications" [1].

Concerning this statement, it should be noted that even the manufacturer of UPA (ellaOne), never stated that side effects are not common, that they are only "mild," or that they do not require any medication. Rather, the manufacturer emphasizes the seriousness of side effects and classifies them into three categories, namely common, uncommon, and rare, as follows:

- Twelve "common" side effects, namely nausea, abdominal (stomach) pain or discomfort; vomiting, painful periods, pelvic pain, breast tenderness; headache, dizziness, mood swings; muscle pain, back pain, tiredness.

- Twenty-five "uncommon" side effects, namely, diarrhoea, heartburn, wind, dry mouth, unusual or irregular vaginal bleeding, heavy/prolonged periods premenstrual syndrome, vaginal irritation or discharge, lesser or greater sex drive; hot flushes; appetite changes, emotional disorders, anxiety, agitation, trouble sleeping, sleepiness, migraine; visual disturbances; influenza; acne, skin lesions, itching; fever, chills, malaise.
- Sixteen "rare" side effects, namely, "genital pain or itching, pain during sex, rupture of an ovarian cyst, unusually light period; loss of concentration, vertigo, shaking, disorientation, fainting; unusual sensation in eye, red eye, sensitivity to light; dry throat, disturbance in taste; allergic reactions such as rash, hives or swelling of the face; feeling thirsty" [8].

In the face of this substantial list of side effects provided by the manufacturer, the WHO seems to belittle the issues of safety when it characterizes side effects as "not common, they are mild, and will normally resolve without further medications" [1]. It should be noted in this context that the WHO denigrated adverse events also in a document published in 2018, entitled "Family Planning. A Global Handbook for Providers" (2018 edition) by stating: "Side effects are not signs of illness and they do not last long. Most women have no side effects" [9]. Paradoxically, at the same time the WHO recommended medication to be used for severe nausea, namely "25–50 mg meclizine hydrochloride (such as Agyrax, Antivert, Bonine, Postafene) one-half to one hour before taking ECPs" [9].

By trivializing the topic of adverse events, the WHO not only contradicts the manufacturer but also such renowned agencies as the FDA. Indeed, the FDA lists several severe adverse events which cannot be considered as "mild." Thus, for Levonorgestrel the FDA specifies: "Some Side Effects - Menstrual changes, Headache, Nausea, Vomiting, Dizziness, Lower stomach (abdominal) pain, Breast pain, Tiredness" [3]. For UPA the most common side effects enumerated by the FDA are: "Headache, Nausea, Abdominal pain, Menstrual pain, Tiredness, Dizziness" [3].

Particular attention deserves the WHO's misleading claim pertaining to the safety of the copper-bearing IUD: "A copper-bearing IUD is a safe form of emergency contraception" [1]. This affirmation is in sharp contrast to recent legal findings. More accurately, the copper-bearing intrauterine device is at present a topical issue in US courts due to the severe harm it has afflicted to thousands of women who were using it. These lawsuits postulate that Paragard had a defective design as well as a manufacturing defect, that the label failed to warn the users, 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" [10].

The most noteworthy aspect of the legal ramifications of the contraceptive device is the date of the initiation of claims against the manufacturer, namely 2016. This means that five years before the WHO emphasized the safety of the copper-bearing IUD, its dangerous design was already known. "Nebraska woman Stephanie Ideus was one of the people who filed a suit against Teva Pharmaceuticals, one of the manufacturers of the device, in 2016. During her Paragard IUD removal, the device broke and imbedded in her uterus, and she required surgery to have it removed, according to her complaint" [11].

Besides heterodoxies on safety and mode of action, the WHO disseminates controversial information on the efficacy of EC.

Efficacy

Concerning efficacy, the WHO presents various data on EC in general, on Ulipristal Acetate (UPA), and on Levonorgestrel (LNG). These data, however, do not harmonize with the estimates proposed by other health authorities, such as the US Food and Drug Administration (FDA). More accurately, the WHO's document on EC indicates a remarkably high efficacy, namely prevention of pregnancy in less than five women among one hundred: "Emergency contraception (EC) can prevent up to over 95% of pregnancies" [1]. In contrast to the WHO's data, the FDA indicates a significantly lower efficacy, namely 12.5 for levonorgestrel: "7 out

of every 8 women who would have gotten pregnant did not become pregnant after taking emergency contraception" [3]. For UPA the FDA indicates and even lower efficacy, namely 34 to 40: "60 to 66% of expected pregnancies were prevented with correct use of ulipristal acetate" [3]. As can be see, both estimates reported by the FDA indicate a lower efficacy than the data reported by the WHO.

The pearl index

What should be noted in the WHO document is the absence of any reference to the Pearl Index (PI). As is commonly known, the Pearl Index (PI) has been defined as, "a statistical estimation of the number of unintended pregnancies in 100 woman-years of exposure (e.g. 100 women over one year of use, or 10 women over 10 years)" [12]. Despite some shortcomings, the PI is still appreciated by scientific research. Thus, a recent publication on digital contraceptives considers the PI as a "well-established technique" and recommends refining it to obtain more reliable results on the effectiveness of the Basal Body Temperature (BBT), one of the natural non-hormonal (or Fertility Awareness-Based) methods: "A well-established technique to characterize the effectiveness of a contraceptive is the Pearl Index. Thus, a relevant question is how the Pearl Index of a given contraceptive can be improved. For the smartphone-based digital contraceptives studied in the present paper, this boils down to the problem of BBT-based fertility detection" [13].

It should be noted that interpretations of the Pearl Index are an ongoing topic in statistical studies. Thus, in response to a guideline released by the European Agency for the Evaluation of Medicinal Products (EMEA), which called for the calculation of a confidence interval for the PI, two statistical models had been suggested. These two models – the Bernoulli model and the Poisson model -- were discussed in a publication from the year 2006, which also drew attention to the difficulty of calculating a confidence interval for the Pearl Index as a statistical parameter. "However, the interpretation of the Pearl Index as a statistical parameter, for which a confidence interval can be calculated, needs further clarification. The guideline does not provide the necessary definitions. In this paper, two statistical models, the Bernoulli model and the Poisson model, are compared; both can be used for the calculation of the Pearl Index and its upper confidence limit" [14].

In light of the world-wide use of the PI it would be advantageous if the WHO indicated its estimates for effectiveness also as PI. This would greatly facilitate comparisons of data on the effectiveness of contraceptive methods on the international level.

As regards comparisons of estimates for efficacy, attention should be drawn to two other documents issued by the WHO. The data indicated in these documents do not dovetail with the WHO's own pregnancy rates of 1.2% for UPA and 1.2% to 2.1% for LNG cited in the document on EC. More accurately, in its Global Handbook for Providers of 2018, the WHO presents estimates for UPA, for progestin only, and for combined estrogen and progestin ECPs [9]. In its own words, the WHO answered the question of how effective EC is by claiming a PI of 8: "How Effective? If 100 women each had sex once during the second or third week of the menstrual cycle without using contraception, 8 women would likely become pregnant" [9]. For UPA and Levonorgestrel, the WHO specifies: "If all 100 women used ulipristal acetate ECPs, fewer than one woman would likely become pregnant. If all 100 women used progestin-only ECPs, one woman would likely become pregnant" [9]. For combined estrogen and progestin ECPs, the WHO specifies: "If all 100 women used combined estrogen and progestin ECPs, 2 women would likely become pregnant" [9]. These estimates presented in the WHO's Global Handbook for Providers, are a replication of the data presented in another document, namely the publication of 2020, entitled Family Planning/Contraception Methods. In this chart-like overview, the WHO specifies that effectiveness data refer to the "pregnancies per 100 women per year with consistent and correct use" [15]. According to this document, effectiveness is less than 1 for UPA, 1 for progestin only, and 2 for combined estrogen and progestin ECPs: "< 1 for ulipristal acetate ECPs. 1 for progestin-only ECPs. 2 for combined estrogen and progestin ECPs" [15].

As is obvious, the WHO's estimates in the publications from 2018 and 2020 do not harmonize with its own data of 2021 and do not blend with the data provided by the FDA, namely 12.5 for Levonorgestrel (LG) and 34 to 40 for UPA [3]. Due to a lack of precision in the WHO's document on EC, it is unclear whether the figure quoted is valid for UPA, for levonorgestrel, for the copper-containing intrauterine device or for the copper intrauterine contraceptive system releasing UPA.

Clearly, the WHO's data on the efficacy of EC are contradictory and do not harmonize with data provided by the FDA. Women whose primary concern is efficacy of the various options for EC cannot rely on data presented by the WHO. Besides the imprecise data on efficacy, neglect of safety, inaccurate statements on the mode of action, the WHO's document is flawed by incompleteness of information.

Lack of completeness

It goes without saying that one of the most important pieces of information for women contemplating EC is knowledge about available options. In enumerating these options, the WHO fails to provide complete information because it omits the copper contraceptive system releasing ulipristal acetate. This copper intrauterine contraceptive system releasing ulipristal acetate has been described in a study of 2021 which discussed 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" [16].

As regards this additional option for EC it is not clear why the WHO failed to take into consideration the findings of the short-term study cited above. After all, it was published already in June 2021, and the WHO document on EC is dated 9 November 2021. If the WHO is indeed committed to "constantly reviewing emerging evidence" [1]. the results of studies that date back several months should be communicated to the consumer.

Political and ethical aspects of EC

As is commonly known, the pharmacological findings concerning UPA as an abortifacient [4]. similar to Mifepristone raise the question of abortion medication. This question has prompted the FDA to issue several documents on the Risk Evaluation and Mitigation Strategies (REMS) program [17,18]. This program, in turn, has been the basis for political efforts to safeguard access to medication abortion for the post-Roe generation in 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" [19].

The ethical dimension of EC pills has been addressed as early as 2014 in one of the most comprehensive and influential reviews on EC. In raising the question of abortifacient properties, this publication stated that even a natural method such as Breast Feeding might have post-fertilization effects and thus be considered as abortifacient. "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, and even 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" [20].

Given the importance of legislative and ethical dimensions of EC it is surprising that the WHO refrains from even mentioning these dimensions. Actually, the WHO apparently seeks to avoid the issue of abortion by denying – in contradiction to scientific evidence -- any abortifacient effects of EC.

Conclusions and Implications

As can be seen from the preceding discussion on the documents on EC emanating from the WHO, the WHO misleads women by inaccurately describing the mode of action and concealing abortifacient potentials. Pertaining to safety, the WHO trivializes adverse events and neglects ongoing lawsuits with regard to the copper-bearing intrauterine device which had afflicted sever injuries to thousands of women in the USA. Concerning efficacy, the WHO fails to provide consistent data which agree with data presented by other health authorities such as the FDA. As to completeness of information, the WHO fails to provide complete information by omitting the copper intrauterine contraceptive system releasing UPA.

Given these results it must be concluded that the WHO cannot be considered a reliable source of information for women seeking advice and guidance on EC. As a consequence, the question arises as to whether the WHO should receive further funding, if the publications disseminated contain inaccurate, incongruent, incomplete, and therefore misleading information.

Conflict of Interest

The author declares no conflicting interests.

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