REVIEW ARTICLE

Pharmacological topics in present-day birth control and contraception

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ABSTRACT

The aim of the paper is to highlight topics pertinent to present-day birth control and contraception. On the background of new developments in the pharmacology of birth control and family planning, the paper discusses their relevance for improving the most efficacious methods of contraception, i.e., Long Acting Reversible Contraception (LARC) and Emergency Contraception (EC). In doing so, it focuses on mechanisms of action and adverse events, and suggests measures to be implemented in the clinical practice according to bioethical principles

Key Words: *Contraception; SPRM; LARC*

Pharmacological aspects of contraception increasingly receive attention owing to the appearance of new products on the market. At present, Long Acting Reversible Contraception (LARC) and Emergency Contraception (EC) are foci of interest because LARC methods are hailed as "the most highly effective" methods of contraception (1), and Emergency Contraception, requiring no compliance similar to traditional oral contraceptives, is recommended as the ultimate chance for preventing an unintended pregnancy (2).

Concerning mechanisms of action, some controversies surround EC, in particular UPA, while adverse events of LARC need additional inquiries. The following discussion aims at shedding light on present-day insights and historical developments in order to clarify the most pertinent questions in present-day use of contraception.

LITERATURE REVIEW

Historical review

Emergency contraception has been a focus of interest for a considerable amount of time. As early as 1995, physiologists had drawn attention to the progesterone antagonist mifepriston for the production of abortion.

"Once conception has occurred, abortion can be produced by progesterone antagonists such as mifepristone" (3). From the same year 1995 date the earliest publications in Pubmed about ulipristal acetate (UPA; then known as 'CDB 2914').

Concerning the chemistry of Mifepristone, known also as RU 486, it has been described as an antigestagen with a five-time greater affinity to the progesterone receptor than progesterone and three times stronger affinity to the glucocorticoid receptor than dexamethasone (4). Internationally, "interceptiva" have been described for post-coitus contraception owing to their ability to inhibit nidation of the zygote: "Postkoitale Kontrazeption durch Hemmung der Nidation (Einnistung) der befruchteten Eizelle" (5).

In Germany, for example, Mifepristone has been admitted only in 1999 as Mifegyne, but not for the indication as a "morning-after-pill" preventing nidation.

In 2011, contraceptive technology stated that EC as "contraceptive pills or insertion of a copper intrauterine contraceptive after unprotected intercourse substantially reduces the risk of pregnancy" and described Ella, Plan B One-Step, and Next Choice as "the only dedicated products specifically marketed for emergency contraception" (6).

In 2013, the Food and Drug Administraton (FDA) included Emergency contraception in the FDA survey of "FDA Approved Methods of Birth Control" and indicated a perfect use failure rate of 85% (7). In 2015, a study dedicated exclusively to Emergency Contraception discussed exhaustively mechanism of action and aspects of safety by providing a definition of safety as "No deaths or serious complications have been causally linked to emergency contraception" (2).

Present-day investigations

At present, more encompassing approaches are used to investigate not only the mechanism of action of EC but also new areas of application. Special attention is devoted to UPA, which was originally designated as a 'progestin antagonist'. At present, however, UPA is considered to be a selective progestogen receptor modulator (SPRM).

"Nowadays, SPRMs are considered progesterone receptor ligands exerting a multitude of unique tissue-selective *in vivo* effects" (8).

SPRMs act as either agonists, antagonists, or combined agonist/antagonists, depending upon the progesterone-sensitive tissue affected by the SPRM. There are a few SPRMs besides mifepristone and UPA that have been or are currently being investigated in clinical trials. Asoprisnil has been tested for treatment of fibroids and menorrhagia, endometriosis, and, in conjunction with estrogen, for post-menopausal therapy. Telapristone acetate has been investigated for fibroids, endometriosis, breast cancer, the treatment of amenorrhea, and renal impairment. As a new class of medication, SPRMs might open new avenues for impacting positively on women's health, and ongoing research focuses on such applications as daily use for contraception, treatment of adenomyosis, endometriosis, and breast cancer. UPA is already established in two important instances, namely as emergency contraception and as treatment for fibroids. UPA is in fact one of the clinically most important SPRMs. Originally it was known as 'the anti-progestin CDB 2914' and was the subject of studies comparable to those regarding the anti-progestin RU 486 or mifepristone. "It was the mifepristone researchers who first proposed the concept of a 'progesterone receptor modulator" (8).

Mifepristone has been used not only for medical abortions, but it was also studied as a potential contraceptive, a treatment of fibroids and endometriosis, and as an anti-glucocorticoid drug. In a similar fashion, CDB-2914 was studied in the 1990s for its antiovulatory and post-coital antifertility properties in both animals and humans.

UPA as emergency contraception–clinical data

Presently available emergency contraception methods include the high-dose, combined estrogen and progestin pill, the insertion of a copper intrauterine device (IUD), the use of levonorgestrel (LNG) at a dose of 1.5 mg, and more recently the administration of oral UPA originally at the dose of 50 mg but now 30 mg.

The most effective method of EC remains the copper IUD. It has the advantage of preventing future contraception, is efficacious and cost-effective, and can be inserted up to seven days after unprotected intercourse, even in a nulliparous woman. However, it does have serious side effects as it may

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increase menstrual blood loss and dysmenorrhoea; in addition, it must be inserted by a professional. It is contra-indicated in women at increased risk of pelvic infection. Among oral hormonal solutions, UPA is more effective than the LNG method or the combined oral contraceptive.

The mechanism of action of UPA is to delay ovulation. UPA prevents ovulation even as luteinising hormone levels are rising. Midluteal phase administration revealed luteolytic activity and a dose-dependent antiprogestin effect on the endometrium. Some authors, therefore, attribute contraceptive (i.e. prevention of fertilization) and contragestive (i.e. prevention of implantation) characteristics to UPA.

Investigations devoted to UPA

Given a variety of treatment possibilities, it seems appropriate that studies continue to investigate additional aspects of selective progestin receptor modulators (SPRMs) including ulipristal acetate, especially with respect to their relevance for the practice of gynecology (8). In a most recent 2017 study, the authors investigate the use of ulipristal acetate (UPA) not only as emergency contraception (EC) but also as a treatment option for symptomatic fibroids in women who want to preserve their fertility or avoid a hysterectomy. When used as an EC, UPA 30 mg is recommended for women, within 102 h of unprotected coitus. As a treatment of fibroids, UPA 5 mg (daily dose) should be administered for periods of three months as a pre-surgical strategy in order to reduce not only bleeding and fibroid size but also to facilitate surgical procedures. Regarding future developments hope is expressed that UPA can be used for other indications such as endometriosis and breast cancer prevention or treatment.

UPA is metabolized via cytochrome P450 3A4, and thus a reduction of efficacy may occur when drugs are used that are known to induce cytochrome induction. These include rifampicin, dabrafenib, enzalutamide, certain anti-epileptic drugs such as primidone, phenytoin or carbamazepine and St John's wort. Whether women who breast feed should use UPA is controversial as it may be excreted in their milk.

In studies comparing efficacy and safety of UPA with levonorgestrel for emergency contraception, authors found that 85% and 69% of anticipated pregnancies, respectively, were averted. In another study, authors concluded that UPA is an effective alternative for emergency contraception, to be used up to five days after unprotected sexual intercourse. Still another study found that women who had repeated unprotected intercourse in the same cycle and obese women had a higher risk of unwanted pregnancy, and women who presented with both risk factors, had the highest rate of pregnancy (8.3% CI: 0.2–38.5%). "Nevertheless, the European Medicine Agency recommends that LNG and UPA be used in women whether they are overweight or not" (8).

One of the most noteworthy results of recent studies is the insight that, contrary to earlier statements, EC can in fact be used repeatedly in the same month, although women who require such repeated use should seek counselling.

Regarding other forms of contraception, attention must be drawn to the pharmaco-dynamic interaction between UPA 30 mg for EC and administration of daily progestin-only contraceptive pill (POP) when initiated the next day. It is thought that initiating the use of a POP (desogestrel (DSG) 0.75 mg) immediately after UPA, limits the ability of UPA to delay ovulation and thus decreases its efficacy as an EC. It seems appropriate, therefore, to delay the start of POP for at least five days after UPA intake in order to preserve the ovulation-delaying effects of UPA. During these five days the regular use of condoms should be imperative.

Safety and adverse events of UPA as EC

According to post-marketing pharmacovigilance data pregnancies occurred in 6.8% of patients using UPA as an EC. When data from both clinical trials and from post-marketing were combined, a total of 376 pregnancies were reported. "For 232 (62%) of them the outcome was: 28 live births (29 newborns), 34 miscarriages, 151 induced abortions, four ectopic pregnancies and 15 ongoing pregnancies at the time of publication" (8).

Although the authors state that "No safety concerns emerged from these data" (8) the EC studies as well as post-marketing data show that UPA was not well tolerated in a number of cases. Among the most frequent adverse events in the clinical studies were headaches "occurring in 19.3% of the cases (vs 18.9% of those using levonorgestrel), and in 6.4% of the post-marketing study population" (8). In the post-marketing study, nausea, abdominal pain and vomiting were the most common symptoms occurring in 13.3% of the patients. Women were advised to use a barrier method of contraception until their next period and were told that during the next menstrual cycle intermittent bleeding could occur.

The findings of the 2017 study described above differ substantially from earlier ones. Thus a 2015 study states that "the exact mechanism of action of UPA is not completely clarified. In particular, it is still poorly understood when it acts as agonist or antagonist of progesterone" (9). Concerning the use of early markers of pregnancy it is admitted that "attempts to identify a molecule that could operate as an early marker of fertilization have not been successful", and this is also true for a protein called the "early pregnancy factor" (EPF). This protein was first described in mice as an immunosuppressive agent and subsequently identified in additional species and humans. The biological features of EPF are considered as an opportunity for diagnosing early pregnancy so that, in the future, it could be a marker to verify UPA's mechanism of action. Given such lack of early markers of fertilization, it is important to keep in mind the hypothesis of abortogenicity of UPA and the ensuing ethical concerns. "The ethical problem arises in considering the possibility of its putative post fertilization effect, based on the assertion that it causes abortion" (9).

LARC methods and the question of safety

In contrast to the above described methods for emergency contraception, the problem of abortogenicity is not predominant in Long Acting Reversible Contraception (LARC), regarded by some authors as "the most highly effective"methods of contraception (1). However, in LARC too, the question of adverse events deserves ongoing scrutiny.

Despite the claim made by advocates of LARC to the effect that "almost all women can safely use IUDs" (1) attention must be drawn to the numerous conditions where this claim cannot be considered valid. As proponents of LARC admit, women should not undergo the insertion of an IUD in cases such as hypersensitivity to copper (use of the copper-containing IUD is precluded) or hypersensitivity to other components of either type of IUD; current pelvic infection or a sexually transmitted disease (STD); gynecologic cancers; current purulent cervicitis or known chlamydial or gonococcal infection; and certain other serious medical conditions.

Regarding unpropitious medical conditions, they are numerous and have been summarized in the "Medical Eligibility Criteria for the Initiation of LARC methods" (1) namely: Distorted uterine cavity (which is incompatible with IUD placement); an anatomical abnormality that distorts the uterine cavity (might preclude proper IUD placement); current pelvic inflammatory disease; gonococcal or chlamydial infection, or purulent cervicitis; postpartum or postabortion sepsis; persistent intrauterine gestational trophoblastic disease (risk of perforation, infection, and hemorrhage); cervical cancer (increased risk of infection and bleeding at insertion ~ the IUD probably must be removed at the time of cancer treatment); endometrial cancer (increased risk of infection, perforation, and bleeding at insertion; need for removal at the time of cancer treatment); unexplained vaginal bleeding (suspicion of serious condition); suspicion of pregnancy or an underlying pathologic condition (eg, pelvic cancer); irregular bleeding patterns (if associated with the method used, it might mask symptoms of underlying pathologic conditions); current breast cancer (hormonal stimulation may worsen the condition); history of breast cancer with no evidence of disease for 5 years; complicated solid-organ transplantation (data on risks and benefits are limited in this population); systemic lupus erythematosus (with severe thrombocytopenia raises concern about an increased risk of bleeding); systemic lupus erythematosus (with positive or unknown antiphospholipid antibodies raises concern about an increased risk of both arterial and venous thrombosis); severe, decompensated cirrhosis (hormonal exposure may worsen the condition); hepatocellular adenoma or hepatic malignancy (hormonal exposure may worsen the condition).

In addition to these 15 conditions which exclude from medical eligibility for LARC there are numerous adverse event, side effects, and risks. Concerning side effects, champions of LARC concede: "A common side effect of using a copper-containing IUD is increased menstrual bleeding" (1). Regarding one of the most perilous complications, namely perforation, it has been admitted that "uterine perforation, although rare, may be more prevalent among women who are breastfeeding" (1). Perforation, however, should be viewed as one of the most feared complications and has been discussed for quite a number of years. As early as 2000 it was recommended to perform an ultrasound immediately following insertion" (5).

Concerning thromboembolism associated with LARC use, proponents hold that conclusive studies are still missing, but regarding expulsion some data are available. These data indicate that the expulsion rates are lowest when

insertion is performed at 4 to 8 weeks post-partum. "Expulsion rates vary widely by study population but are generally lower when the IUD is inserted immediately after delivery of the placenta (3% to 27%) than when it is inserted 10 minutes to 48 hours after delivery of the placenta (11% to 27%); both rates are higher than those with standard insertion at 4 to 8 weeks post-partum (0% to 6%)" (1).

DISCUSSION

Regarding adverse events associated specifically with implants, studies have brought to light a number of conditions, besides bleeding as the primary complication. "The most common adverse events besides unscheduled bleeding that were deemed possibly, probably, or definitely related to the etonogestrel implant included headache (16%), weight gain (12%), acne (12%), breast tenderness (10%), emotional lability (6%) and abdominal pain (5%)" (10). In the case of depot medroxyprogesterone acetate (DMPA), another progestin-only contraceptive that reduces estrogen levels, decrease of bone mineral density has been confirmed.

CONCLUSION

As the foregoing discussion has shown, new insight has been gained in the area of emergency contraception, especially for ulipristal acetate and its novel possibilities of application in the practice of gynecology. Regarding mechanism of action, the controversy of contraceptive versus contragestive properties is still unresolved. As far as LARC is concerned, contraindications and adverse events must receive heightened attention, despite assertions made by some authors that "all women can safely use"this kind of contraception (1).

IMPLICATIONS

In view of a considerable number of contraindications for both Emergency Contraception as well as LARC the needs of those women who do not tolerate drugs and devices must be heeded, in addition to those women who prefer, for whatever reasons, as for example fear of abortion, non-hormonal contraception. Given noteworthy estimates for some of the natural non-hormonal methods (6) women should receive counseling in the doctor's office also on such methods as symptothermal, Ovulation, TwoDay, and Standard Days method. After all, comprehensible and encompassing information, according to each woman's needs and convictions, is a central requirement of the Code of Medical Ethics: "The patient's right of self-decision can be effectively exercised only if the patient possesses enough information to enable an intelligent choice" (11).

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