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# Mechanism of Action, Efficacy and Safety of Emergency Hormonal Contraception (levonorgestrel and ulipristal acetate) and Attitudes of Pharmacists

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## SUMMARY

Emergency hormonal contraception is used to prevent unintended pregnancy postco- itally. The mechanism of action of the most frequently used hormonal preparations for emer- gency contraception, levonorgestrel (LNG) and ulipristal acetate (UPA), is still not fully known, but clinical trials indicate that they act by inhibiting or delaying ovulation. LNG has a long history of use for emergency contraception, proven safety and high efficacy if administered in the preovulation period. The newest emergency contraceptive, UPA, available only with a prescription, is indicated within this period of 120 hours after sexual intercourse and the data indicate that UPA does not lose efficacy within this period. Clinical trials showed its non- inferiority versus LNG and its effect on the potentially occurring pregnancy is being addition- ally monitored. However, many misconceptions and controversial opinions about emergency contraception are still present, even among pharmacists. A search of Medline database iden- tified 20 papers published from January 1993 to December 2012, on pharmacists' know- ledge, attitudes and practices related to emergency contraception. In these papers, the atti- tudes of pharmacists pertaining to the dispensing regime of emergency contraception were different. Research in Australia has shown that personal attitudes and religious convictions influence the practice of dispensing emergency contraception. In the research conducted in New Mexico, 30% of pharmacists were against prescribing emergency contraception for reli- gious or moral reasons. There were no published data in regards to pharmacists' knowledge, attitudes and dispensing practice in Serbia and such research is highly recommended.

**Key words:** emergency contraception, levonorgestrel, ulipristal acetate, pharmacist

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## INTRODUCTION

Emergency hormonal contraception is administered with the goal to prevent unintended pregnancy after unprotected sexual intercourse or missed/unsuccessfully administered regular method of contraception. Emergency hormonal contraception prevents fertilization and thus is not an abortifacient, as according to medical criteria pregnancy begins with the implantation of the fertilized ovum (1). The *Yuzpe* method was named after a Canadian gynecologist who was the first to administer in the 1970s a combination of 250  $\mu\text{g}$  levonorgestrel (LNG) and 50  $\mu\text{g}$  ethinyl estradiol in two doses as emergency hormonal contraception. Today, this method is less frequently used because levonorgestrel only based emergency contraception is more efficient and because estrogen component more often leads to adverse effects, primarily nausea, headache and painful breast tenderness (2). In the 1990s, two doses of LNG of 0.75 mg began to be applied for emergency contraception, which proved to be a more efficient and safer method than *Yuzpe*'s; nausea appears in approximately 16% of cases vs. 46% and vomiting in 2.7% vs. 22.4% (3). There are two types of LNG preparations; with 0.75 mg LNG in the case of which the first tablet is taken within the interval of 72 hours of sexual intercourse, and the second 12 hours later, and LNG with 1.5 mg LNG which is administered as a single dose, which is more practical. Because of its proven safety and high efficacy, LNG is regarded as the "golden standard" of emergency contraception (4). In certain countries, e.g. China and Israel, mifepristone, a competitive progesterone antagonist, is also used for emergency contraception. However, in most countries, mifepristone use led to great social problems, because in higher doses it used to induce medicament abortion (5). The latest preparation belonging to this group, ulipristal acetate (UPA), was approved for use in Europe in 2009, and in 2010 in the United States of America (USA) and Serbia. It is indicated within 120 hours after sexual intercourse, and clinical trials showed its non-inferiority versus LNG (6).

Today, preparations for emergency contraception are available in over 140 countries (7). Broader administration of emergency contraception prevents numerous abortions, thus users have direct access to LNG tablets in nine countries (Bangladesh, Bulgaria, Canada, India, Laos, the Netherlands, Norway, Sweden and the USA). In over 60 countries, pharmacist can dispense LNG without prescription (e.g. in Australia, Austria, Great Britain, Spain, Slovenia, Serbia, Bulgaria, and others) (7). No matter if emergency contraception is obtained with or without prescription, pharmacists can considerably influence the scope and adequate use of these preparations. However, moral, ethical or religious convictions of the pharmacist can oppose the use of emergency contraception. Thus, in some countries, as in the USA, pharmacist can refuse to dispense emergency contraception to the users (8). In such cases, the pharmacist must act

professionally and as soon as possible, without condemning, direct the user to another pharmacist who will dispense her emergency contraception. These pharmacists should also timely inform their colleagues and employers about similar situations and possible consequences.

## AIMS

The aim of this paper was to review the practice, knowledge and attitudes of pharmacists pertaining to emergency hormonal contraception as well as the latest data on the mechanism of action, efficacy and safety of the most frequently used emergency hormonal contraceptives, LNG and UPA.

## MATERIAL AND METHODS

From January to March 2013, Medline database was searched to find papers published from January 1993 to December 2012, presenting data pertaining to knowledge, attitudes and practice of pharmacists in connection with the dispensing and use of emergency hormonal contraception. Papers published in Serbian and English were taken into consideration. The following key words and Mesh terms were used for the search: contraception, postcoital, emergency contraception, contraceptives, contraceptive agents, pharmacist, pharmacy, knowledge, attitudes, practice. Papers from the obtained list were reviewed. In addition, references were reviewed and additional papers were included.

## RESULTS AND DISCUSSION

### Mechanism of action and time of administration of emergency contraception

#### *Levonorgestrel*

The exact mechanism of action of LNG is not fully known, but it is believed that LNG inhibits or delays ovulation, i.e. the effect of LNG postpones the development and maturation of follicles, inhibits rupture and formation of the persistent follicle. If it is administered before the level of the luteinizing hormone (LH) begins to rise in mid-cycle, the process of ovulation can be inhibited or delayed for the next 5-7 days, which is a sufficiently long period for spermatozoa present in the female genital tract to become inactive (9). If the LNG tablet is administered closer to the time of ovulation, prevention of ovulation is less probable. It has been established that LNG has no effect if administered immediately before ovulation, and it is also considered to be ineffective after fertilization (10). Clinical trials confirmed that LNG does not influence the process of implantation of the embryo in the endometrium, nor has any significant effect been noted on oviduct motility (11).

### Ulipristal acetate

UPA is a synthetic selective progesterone receptor modulator with a high binding affinity that thus prevents or delays ovulation (12). Clinical trials have shown that in over 60% of women UPA administration led to delay of ovulation by a minimum of 5 days (13). UPA efficacy depends on the time of administration; if it is administered before the level of LH begins to rise, ovulation is postponed by a minimum of 5 days in 100% of subjects. If UPA is administered in the rising phase, but before the LH peak is reached, in 78.6% of women ovulation is postponed by minimum 5 days. However, if it is administered after the LH peak is reached, ovulation is postponed in 8.3% of women (14, 15). It was shown that UPA also leads to changes in the endometrium, but it is still not clear if this causes inhibition of implantation (16), thus it is considered that the activity of UPA is primarily based on delaying of ovulation.

### Efficacy and safety

One of the proposed parameters for determining the efficacy of emergency contraception is the so-called prevented fraction, obtained by subtracting the quotient between the number of registered pregnancies after the administration of emergency contraception and the number of pregnancies without the use of emergency contraception. The prevented fraction is the number of pregnancies avoided by administering emergency contraception (17). In evaluation of efficacy of EC there are many problems such as the exact time of ovulation, which is often not known, some women do not recall when they had the last menstrual cycle and/or when the unprotected intercourse occurred, whereas some women are already pregnant when emergency contraception is administered. The fertile ability of concerned woman and man is unknown as well. Using the same evaluation method that was used for LNG and UC made comparison of their efficacy possible.

LNG is efficient if it is administered within the first 72 hours after sexual intercourse, but it is still unclear if its efficacy declines during this time interval. Analysis of results of four randomized trials performed by the World Health Organization (WHO) established that there is no

statistically significant difference in the rates of pregnancy after the administration of LNG on days 2, 3 or 4, compared to day 1 (18). It has also been proven that the efficiency of UPA does not decline if it is administered after a longer period of time after sexual intercourse if 120 hours have not lapsed (6, 19). In the meta-analysis that compared the efficiency of UPA and LNG, depending on the time of administration within the interval between 0 and 120 hours, *Glasier et al.* showed that the pregnancy rate was statistically significantly lower in the group of women who used UPA compared to LNG (Table 1) (6).

After the administration of LNG and UPA there was no statistically significant difference in the type and frequency of adverse reactions (Table 2) (6). After LNG administration slightly under 20% of women experienced nausea, whereas vomiting occurred in only 1% of users (20). When dispensing emergency contraception it is important to counsel users about repeating the dose of the preparation if vomiting occurs within three hours after administration (12, 21). In addition, users should be informed about the possibility of a transient disturbance of the rhythm of menstrual bleeding. However, if no bleeding appears within three weeks after using emergency contraception, or if menstruation is late by more than a week, users should be advised to take a pregnancy test (22).

It is regarded that administration of repeated LNG doses is safe and efficient, so that it can also be used more than once during one cycle (23). As opposed to LNG, UPA should not be used more than once during one menstrual cycle (12).

The few data obtained from epidemiological studies have not indicated that LNG had any harmful effect on the fetus if pregnancy occurs in spite of the administration of emergency hormonal contraception (21). However, it is not known how UPA influences the course and outcome of pregnancy. Since this is a rather new preparation for emergency contraception, its adverse reactions are carefully monitored. There is a European Register for monitoring pregnancy outcome in women who had used UPA. Patients and healthcare professionals should be encouraged to report all cases of adverse reactions caused by UPA administration (12).

**Table 1.** Meta-analysis of efficacy of ulipristal acetate and levonorgestrel (6)

| Time (hours) from unprotected sexual intercourse to intake of emergency contraception | Pregnancies, n/N (%) |                | Odds ratio (95% CI) | p-value |
|---|----------------------|----------------|---------------------|---------|
|   | UPA                  | LNG            |                     |         |
| 0-24  | 5/584 (0,9%)         | 15/600 (2,5%)  | 0,35 (0,11 - 0,93)  | 0,035   |
| 0-72  | 22/1617 (1,4%)       | 35/1625 (2,2%) | 0,58 (0,33 - 0,99)  | 0,046   |
| 0-120   | 22/1714 (1,3%)       | 38/1731 (2,2%) | 0,55 (0,32 - 0,93)  | 0,025   |

**Table 2.** Frequency of adverse reactions in levonorgestrel and ulipristal acetate users (6)

| Adverse reaction     | LNG users |      | UPA users |      |
|----------------------|-----------|------|-----------|------|
|                      | n         | %    | n         | %    |
| Headache             | 211       | 18,9 | 213       | 19,3 |
| Dysmenorrhoea        | 160       | 14,3 | 142       | 12,9 |
| Nausea               | 126       | 11,3 | 141       | 12,8 |
| Fatigue              | 44        | 3,9  | 61        | 5,5  |
| Dizziness            | 55        | 4,9  | 57        | 5,2  |
| Abdominal pain       | 75        | 6,7  | 56        | 5,1  |
| Upper abdominal pain | 46        | 4,1  | 37        | 3,3  |
| Back pain            | 27        | 2,4  | 35        | 3,2  |

### Knowledge, attitudes and practice of pharmacists regarding emergency contraception

We identified 20 papers on the pharmacists' knowledge, attitudes and practice in regards to emergency contraception, and considerable differences were not found. For example, in a research performed in 1997 in South Africa, 69% of pharmacists support the dispensing of emergency contraception without prescription, while 67% believe that this is important for increasing the level of public awareness about this type of prevention of unintended pregnancy (24). On the contrary, the research performed by *Barett* and Harper in 1996 in Great Britain among pharmacists in public pharmacies and general practitioners revealed a negative attitude regarding the regime of dispensing these medicines without prescription (25). Research performed in Sweden in 2002 showed that 70% (153) of pharmacists and 68% (91) of physicians considered that it is indispensable to establish adequate cooperation between pharmacies and clinics on the issue of emergency contraception. Pharmacists need advice and support of experienced professionals, especially in cases pertaining to teenagers. Physicians feel that pharmacists should offer users adequate information about local clinics that can further monitor and counsel them, and in specific cases refer patients to them (26). Personal attitudes and religious beliefs of pharmacists can influence their practice. Research performed in Australia from December 2008 to January 2009 showed that 22% (92/418) of pharmacists from public pharmacies considered reasonable that religious beliefs of the pharmacists influence their decision to dispense emergency contraception. In this research, 75.1% of pharmacists occasionally refused to dispense emergency contraception most frequen-

tly because someone else came to the pharmacy instead of the intended user (59.7%), the user was under 16 years of age (35.1%), and more than 72 hours had passed after unprotected sexual intercourse (30%). Advanced provision of emergency contraception to any women under any circumstances was unacceptable for 69% of pharmacist, to parents of intended users for 63.9% of pharmacists and users under 16 years of age for 71.7% of pharmacists. Of the total number of interviewed pharmacists, 65.2% had training for counseling relevant to dispensing emergency contraception. Pharmacists most often counseled users about the dosage (91.8%), adverse reactions (90.2%), and efficacy of emergency contraception depending on the time lapsed from unprotected sexual intercourse to the time of administering emergency contraception (88.8%). Among interviewed pharmacists 81.9% agreed that when dispensing emergency contraception, it is their task to counsel the user about regular contraception, but only 54.5% felt that users should also be offered advice about sexually transmissible infections. Pharmacists in this research stated that the lack of privacy was a barrier for adequate counseling the user. Many stated that they counseled users only in isolated parts of the pharmacy where it was possible to provide privacy or in a place at a distance from other patients (27). Research performed in Turkey in 2008 showed that 98% (539/551) of pharmacists had experience with dispensing emergency contraception, and 70% stated that they occasionally dispense it also to men. Generally, most pharmacists had a positive attitude toward the existence of emergency contraception and felt that its use is ethical. To the question if their pharmacy had a space for counseling where privacy is secured, 75% answered affirmatively, 80% of female pharmacists and 66% of male pharmacists. At the same time, 79% confirmed that they feel comfortable to offer advice on contraception, while 16% stated that they were comfortable only if

the patient was of the same sex. Advice most frequently offered by pharmacists in Turkey pertained to the time period when tablets are taken (89%), dosage (86%), efficacy (73%), pregnancy test (63%), adverse reactions (50%) and methods of contraception (48%). The main sources of information about emergency contraception for pharmacists were representatives of pharmaceutical companies (53%) and continuous education programs (26%). It is presumed that female pharmacists know more about emergency contraception from personal experience, so they offer advice more often, and feel more comfortable during the process than men. Because of cultural influences in Turkey, certain male pharmacists did not feel comfortable when offering advice on emergency contraception. Pharmacists in this research were generally against dispensing emergency contraception with a prescription only, while 58% felt that the dispensing of emergency contraception should be limited only to persons over 18 years of age (28).

According to the results of research conducted among 523 pharmacists in New Mexico in 2004, the main challenges that pharmacists had to overcome in their practice when dispensing emergency contraception were: the lack of insight into the patient medical history, no follow-up on efficacy of emergency contraception, lack of time and lack of a private space for counseling. Some 30% of pharmacists in this research were against prescribing emergency contraception for religious or moral reasons. Almost 25% of responders agreed with the statement that emergency contraception is a form of abortion. As opposed to 76% of pharmacists who stated that they would refer patient to another pharmacist who would provide emergency contraception if their employer would not permit them to dispense it themselves, 24% of pharmacists would not provide it or refer the patient to another pharmacist. Results of this research additionally strengthened the debate pertaining to the right of a pharmacist to refuse to dispense emergency contraception with moral objection (29).

There were not published data on the pharmacists knowledge, attitudes and dispensing practice in Serbia and such research will be of a high interest for medical professionals, emergency contraceptive users and reproductive health of women in Serbia. In pharmacies in Serbia both most popular preparations for emergency contraception, LNG and UPA, are available. LNG is dispensed without prescription to users over 16 years of age, while LNG use is not recommended for users under 16 years of age without medical supervision (21).

UPA is dispensed only with a prescription (12). There is no published data how often pharmacists in Serbia dispense emergency contraception, if they provide counseling. Often frequent users of emergency contraception are teenagers and young nulipara women whose reproductive health should be protected. Considering the fact that one of emergency contraception preparation is available without prescription, pharmacists are the only ones who are in contact with the users, so thus their attitudes and advices given to the patients are very important.

## CONCLUSION

Emergency contraception is a second chance for women to prevent pregnancy at the time when regular contraception fails, or when it is not used. Efficacy and safety of LNG has been demonstrated during many years of use. In addition, there is a new product, UPA, that proved in clinical trials to be at least as effective as LNG, and whose influence on a potential pregnancy is still being monitored. Since pharmacists are the healthcare professionals most accessible to users, their role is of key importance for adequate administration of these products. However, from investigations in other countries it is evident that the knowledge and personal attitudes of pharmacists can influence their practice when dispensing emergency contraception and sometimes also lead to users being denied the preparation. There is no published data about the status in Serbia relevant to this issue. Therefore, the recommendation is to conduct research about the knowledge, attitudes and practices of pharmacists regarding emergency hormonal contraception.

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## MEHANIZAM DEJSTVA, EFIKASNOST I BEZBEDNOST HITNE HORMONSKE KONTRACENCIJE (LEVONORGESTRELA I ULIPRISTAL ACETATA) I STAVOVI FARMACEUTA

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### Sažetak

Hitna hormonska kontracepcija se koristi za sprečavanje neželjene trudnoće postkoitalno. Mehanizam dejstva najčešće korišćenih preparata hitne kontracepcije, levonorgestrela (LNG) i ulipristal-acetata (UPA) još uvek nije u potpunosti poznat, ali klinička ispitivanja ukazuju da je u pitanju inhibicija ili odlaganje ovulacije. Za hitnu kontracepciju dugo se koristi LNG, jer ima dokazanu bezbednost i visoku efikasnost, ukoliko se primeni u periodu pre ovulacije. Najnoviji preparat iz ove grupe, UPA, koji se izdaje samo na recept, može se primeniti u periodu od 120 sati nakon seksualnog odnosa. U kliničkim ispitivanjima se nije pokazao lošijim u odnosu na LNG, a njegov uticaj na eventualno nastalu trudnoću se dodatno prati. Podaci ukazuju na činjenicu da UPA ne gubi na efikasnosti u periodu od 120 sati. Međutim, prisutne su mnoge zablude i kontroverzna mišljenja o hitnoj kontracepciji, čak i među farmaceutima. Pretraživanjem Medline baze podataka nađeno je 20 radova objavljenih u periodu od januara 1993. do decembra 2012. godine koji razmatraju znanje, stavove i praksu farmaceuta u vezi sa hitnom kontracepcijom. U ovim radovima se stavovi farmaceuta razlikuju po pitanju režima izdavanja hitne kontracepcije. Istraživanje u Australiji pokazalo je da lični stavovi i religijska uverenja utiču na način izdavanja hitne kontracepcije. U istraživanju u Novom Meksiku 30% farmaceuta je bilo protiv propisivanja hitne kontracepcije iz religioznih ili moralnih razloga. Među pronađenim radovima nije bilo podataka o istraživanjima iz Srbije. Preporuka je da se sprovedu istraživanja o znanju, stavovima i praksi farmaceuta u vezi sa hitnom hormonskom kontracepcijom u Srbiji.

**Ključne reči:** hitna kontracepcija, levonorgestrel, ulipristal-acetat, farmaceut