Investigating the epidemiological factors, efficacy and side effect profile of emergency contraception

Ph.D. thesis

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1. Introduction

Over half of all pregnancies are unintended, resulting in a substantial global burden of induced abortions, as reported by the World Health Organization (WHO). To mitigate this, it is essential to have a comprehensive understanding of contraceptive methods and their effective utilization. Particularly, emergency contraception plays a pivotal role as an easily accessible option for preventing unintended pregnancies. By employing emergency contraception and promoting awareness of postcoital contraception, the incidence of unintended pregnancies could potentially decrease by 75%.
Emergency contraception refers to a form of contraception, such as pills or intrauterine devices (IUDs), that is utilized to prevent unintended pregnancies following unprotected sexual intercourse.

2. Objectives

The use of emergency contraceptives can be influenced by several epidemiological factors. Age, socioeconomic status, education level, and relationship status can play a role in the use of emergency contraception.
Our current knowledge regarding the impact of personal factors and sexual behaviors on the utilization of emergency contraception is limited.

We aimed:

1) to provide an up-to-date overview of the previously and currently used methods of emergency contraception, their effectiveness, and practical application
2) to investigate the elucidation and comprehension the factors that promote women to seek emergency contraception immediately after intercourse.

3. Methods

3.1. Emergency contraception- systematic review of the literature

3.1.1. Literature search and study selection in the systematic review

For this literature review, we conducted a systematic literature search using the MEDLINE (PubMed), Embase, and Scopus databases, following the methodology employed in previous systematic literature reviews published in the Orvosi Hetilap. The search was limited to clinical publications in English and Hungarian languages, independently performed by two reviewers, covering the period between 1960 and 2023. The literature search was conducted using predetermined MeSH-compatible keywords and phrases (such as "emergency contraceptive" or "emergency contraception" or "oral emergency contraception" or "mifepristone" or "morning after-pill" or "postcoital contraceptives" or "hormonal postcoital contraceptive" or "progestin-only pill" or "ulipristal acetate" or "intrauterine device" or "IUD" or "Cu-IUD" or "LNG-IUD" or "Copper IUD" or "IUD in emergency" or "synthetic postcoital contraceptive") (Figure 1). Editorials and letters were excluded due to their low level of evidence. Studies conducted without ethical approval were not included in the analysis.

Following the exclusion of duplicates, title and abstract screening were performed, followed by full-text retrieval. Manuscripts in languages other than English and Hungarian, studies involving non-human models, and publications comparing emergency contraceptives with long-term contraceptives were excluded.

3.1.2. Methodological evaluation of the studies in the systematic review

The examined studies were evaluated based on various methodological criteria. The criteria we considered were as follows:

a) Clearly defined study objectives.

b) Adequate sample size for drawing statistical conclusions.

c) Sufficiently informative follow-up period (at least 1 month).

d) Primary outcome variables included the Pearl Index or the number of pregnancies despite medication.

e) The studies provided detailed information on adverse events and side effect profiles.

3.2. Retrospective observational study - Motivators for emergency contraception

3.2.1. Patients in the Hungarian database

This present retrospective observational study is embedded in the MEEC (Motivation and Epidemiology of Emergency Contraceptive Pill) based on the study cohort of a Hungarian data bank containing follow-up data of 455 women. Between July 2021 and September 2021, altogether 455 patients registered on the telemedicine consultation platform 'esemenyutan.hu', where patients with Hungarian health insurance could be prescribed an emergency contraceptive after consulting a gynecologist. As a part of the service, a consultation was provided, and the medicine was prescribed within an hour after the consultation. During consultation, each patient was asked to answer a set of standardized questions to explore their sexual behaviors and lifestyle.

3.2.2. Characteristics

This analysis used the chart review of all these patients, which included the following variables: sociodemographic characteristics: age (calculated by subtracting the date of birth from the date of consulting) and relationship status (married/in a relationship/no relationship).

The questionnaire also included the following gynecological characteristics: description of the intercourse (the exact day and hour of the intercourse, the time elapsed between the registration and the intercourse, and the method of contraception); the first day of the last menstrual period and the number of days since the last menstrual period; past pregnancies (number of pregnancies, abortions, and miscarriages); and the year of the last Pap smear.

The study was approved by the Institutional Review Board of Semmelweis University (SE RKEB: 125/2022).

3.2.3. Data management

The data were quality controlled for repeat consulting (two repeats) (only first visits were kept), and data entry errors.

A binary age variable was created as aged above vs. below 30 years. Patients were divided into groups based on the day of the intercourse being near the ovulation or later in the cycle. The proximity to ovulation was defined as being between days 12–16 in the cycle, considering that the cycle was regular and about 28 days long. The method of contraception was divided into the following groups: using condoms, not using any contraception, and other (including but not limited to any oral contraceptive

[OAC] with days missed, or a contraceptive ring that had been out for too long, or failed interruption of the intercourse).

3.2.4. Statistical analysis

The Shapiro-Wilk test was used to test the normality of continuous variables. Continuous data were described as medians and interquartile ranges given that all variables were non-normally distributed. The Mann-Whitney test was used to analyze the relationship between time since last intercourse, and age, relationship status, history of pregnancies, history of abortions, and proximity to ovulation. The chi-square analysis was performed to assess the correlation of the method of contraception and age, relationship status, history of pregnancies, history of abortions, and proximity to ovulation. Multivariate logistic regression analysis was used to predict the relationships between dependent (time) and independent variables (protection (yes/no), time of ovulation, history of pregnancies (yes/no), being in a relationship (yes/no) and age. The dependent variable (time) received a value of 1 if the patients registered on the website within 24 hours, and a value of 0 if it was over 24 hours.

Statistical significance was set at $p<0.05$. Prism9 GraphPad (ver. 8. GraphPad Software, Inc., San Diego, CA, USA) and SPSS Sigma Stat software were used for data management and analysis, and for creating figures.

4. Results

4.1. Emergency contraception- systematic review of the literature

4.1.1. Search results of systematic review

As a result of the keyword search, we found 8933 studies. After the elimination of duplicates and the selection based on title and abstract, we further examined 135 relevant studies. Out of these, we excluded an additional 112 studies from our review due to incomplete information on drug treatment. Finally, we included 23 clinical trials in our systematic literature review.
These 23 studies, that we have selected cover the entire spectrum (Dienestrol, Diethylstilbestrol, Levonorgestrel, Mifepristone, Mifepristone+Tamoxifen, Ulipristal acetate, Yuzpe-protocol, Copper IUS, GyneFix, LNG-IUS) of emergency contraceptives. Some studies analyzed the effectiveness of oral emergency contraceptives, while several studies gave a scientific treatise on the Copper-IUD.

4.1.2. The efficacy and side effect profile of emergency contraceptive protocols

Although Yuzpe preparations are not available in Hungary, it is important to mention that the pregnancy rate in the studies we reviewed ranged from 1.2% to 2.6% for the Yuzpe protocol.
For LNG, both the studies with two doses of 0.75 mg and the studies with a single dose of 1.5 mg were included in the systematic review. Some studies found a significantly lower estimated efficacy rate for the lower dose of LNG (86.8%) compared to the higher dose (92.99%). However, other studies did not find a difference in efficacy (risk difference of 0.7%). The pregnancy rate ranged from 0.57% to 1% in the examined studies, indicating that LNG was more effective than Yuzpe. It

is important to note, however, that using LNG multiple times within one menstrual cycle (1.5 mg LNG after each intercourse, up to a maximum of 6 times) significantly increases the pregnancy rate, with a pregnancy rate of 4.4% in typical use.
For mifepristone, the pregnancy rate was around 1%, and there was no difference in efficacy when compared to LNG or the combination of mifepristone and tamoxifen in the studies we reviewed. When comparing mifepristone with the Yuzpe protocol, the pregnancy rate was 0% for mifepristone and 1% for Yuzpe (not significantly different).
UPA proved to be more effective than LNG: 85% of pregnancies were avoided with the use of UPA, compared to 69% with LNG. Furthermore, the pregnancy rate was 1.8% for UPA and 2.6% for LNG. The effectiveness of UPA does not decrease with an increase in time (48 vs 120 hours).
Generally speaking, side effects of orally administered emergency contraception methods are mild and rare. The most common side effects include nausea, vomiting, headache, breast tenderness, and menstrual irregularities.
In the case of the Yuzpe protocol (not available in Hungary), the most common side effect is nausea (37-52%), followed by vomiting (21%) and breast tenderness (12%), while bleeding disorders occur in a small percentage of cases. Dienesgestrol causes few side effects (nausea, chest discomfort in 6% of cycles). For diethylstilbestrol, nausea occurs in 44% of cases, no side effects occur in 31.5% of cases, and the menstrual cycle does not change in 40% of cases. Similarly, nausea is the most common side effect for LNG. When comparing lower-dose (2x0.75 mg) LNG to higher-dose (1x1.5 mg) LNG, some studies report a higher occurrence of headaches, breast tenderness, and heavy menstrual bleeding with the higher dose, while others find no difference in the side effect profile. When LNG is administered multiple times within one cycle (up to six times), headaches occur in 15% of cases, while nausea and abdominal

pain occur in 6% of cases. The most common side effect of UPA is headache (20%), followed by nausea (13.6%), menstrual disorders (10.1%), and abdominal pain (9.6%). Mifepristone, either alone or in combination with tamoxifen, causes few side effects, and their frequency is quite similar. When using UPA, the side effects are distributed as follows: 9.5% headache, 9.2% nausea, 6.8% abdominal pain, 4.1% menstrual disorders, 3.5% dizziness, and 3.4% fatigue. The cycle length increased by an average of 2.8 days, while the duration of menstrual bleeding did not change.

When comparing LNG to the Yuzpe protocol, nausea, vomiting, and fatigue occur significantly more frequently with the Yuzpe protocol. Fewer side effects were reported with mifepristone compared to the Yuzpe protocol (nausea 40% vs. 60%, vomiting 3% vs. 17%), but menstrual disorders were more common with mifepristone (42% vs. 13%) (16). When comparing mifepristone to LNG, there is also no difference in the occurrence of side effects. When comparing UPA to LNG, nausea occurs slightly more frequently with UPA than with LNG (29% vs. 24%), but the frequency of other side effects is similar.

In terms of side effect profiles, there is no difference among intrauterine devices. For Copper IUD, changes in bleeding pattern occurred in 32% of patients, and specifically, spotting was observed with IUDs inserted during the ovulatory period (30). When comparing Copper IUD to LNG-containing IUD, there was no difference in the frequency of side effects. Compared to orally administered medications, intrauterine devices are associated with a higher percentage of irregular menstrual bleeding and abdominal pain.

4.1.3. The weight as a factor influencing decision-making

The intake of levonorgestrel preparations is not recommended for individuals with a body weight of 75 kg or a BMI of 25 and

above. In such cases, the German guidelines recommend the use of UPA. In individuals with a BMI of 30 and above, the use of UPA was associated with a twofold increase in the likelihood of pregnancy. Moreover, if there were multiple unprotected intercourse events during the menstrual cycle, obese women had a fourfold increase in the rate of pregnancy.The efficacy of orally administered contraceptives is lower in women with higher body weight compared to what is observed with intrauterine devices, with the latter being the safest method in this specific population group.

4.1.4. Breastfeeding

Levonorgestrel preparations can be safely used during breastfeeding, as the clinically insignificant amount of the active ingredient is excreted into breast milk. Breastfeeding as a contraceptive method (Lactational Amenorrhea Method, LAM) supplemented with LNG counseling and LNG tablets (as needed) resulted in significantly more women starting regular contraception within 6 months compared to women using only the LAM method. Pregnancy occurred significantly more frequently in the LAM-only group (5%) compared to the 0.8% in the LAM+ LNG group. In the case of mifepristone, the highest concentration of the drug in breast milk was observed 12 hours after drug intake. The calculated relative infant dose was 1.5%, indicating that breastfeeding can safely continue without interruption when using mifepristone.

4.2. Retrospective observational study - Motivators for emergency contraception

4.2.1. Description of the sample in the retrospective cohort study

The median age of the 455 patients was 30 years (interquartile range: 25-37). The median time elapsed since the intercourse was 14 hours (interquartile range: 5-32). The median days since

the first day of the last menstrual period was 14 (interquartile range: 10.75-19.92).
Altogether 59.3% (n=270) of patients reported condom rupture, 29.5% (n=134) no protection and 11.2% (n=51) other reasons; 74.1% (n=337) of all patients had no history of pregnancy, 25.9% (n=118) had been previously pregnant, and 5.5% (n=25) of them had at least one abortion. Overall, 70.1% (n=319) indicated being in a relationship, and 29.9% (n=136) reported a one-night stand.

4.2.2. Relationship between time since intercourse and patient characteristics

Those who had used condoms registered after a significantly shorter time than those without protection (p=0.032) or those using another type of protection (p=0.048, Figure 1. In addition, a significantly shorter elapsed time was observed in patients with a history of a previous pregnancy as well (p=0.004, Figure 2).

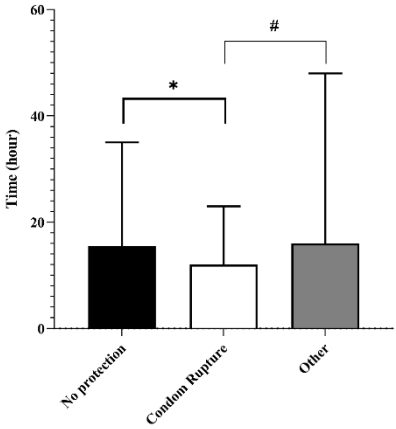

Figure 1. Data are presented as median with interquartile range. Kruskal-Wallis test with Dunn's post hoc test. *p=0.032 Condom Rupture vs No Protection; #p=0.048 Condom Rupture vs. Other

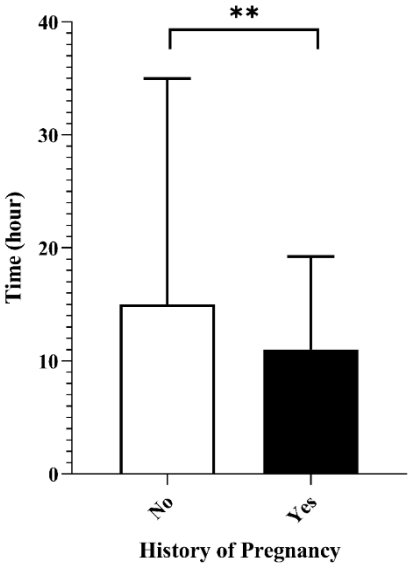

Figure 2. Data are presented as median with interquartile range. Mann-Whitney test. **p=0.0052 history of a previous pregnancy vs. no pregnancy in history

4.2.3. Factors influencing emergency contraceptive request

The logistic model analysis showed that the use of any protection (condom, withdrawal, other) significantly increased the risk of EC request (odds ratio = 1.757, 95% confidence interval: 1.137-2.715; p=0.011); furthermore, a previous pregnancy also significantly increased the risk of EC request (odds ratio = 1.858, 95% confidence interval: 1.063-3.248; p=0.03) Figure 3, Figure 4)

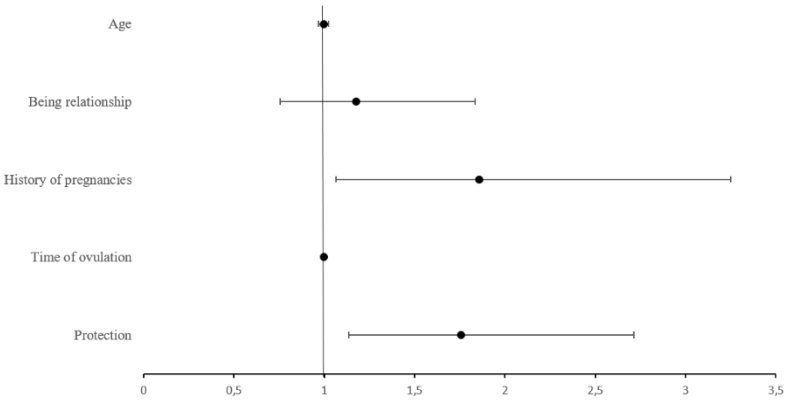

Figure 3. Forest Plot of Odds ratios for request of EC.

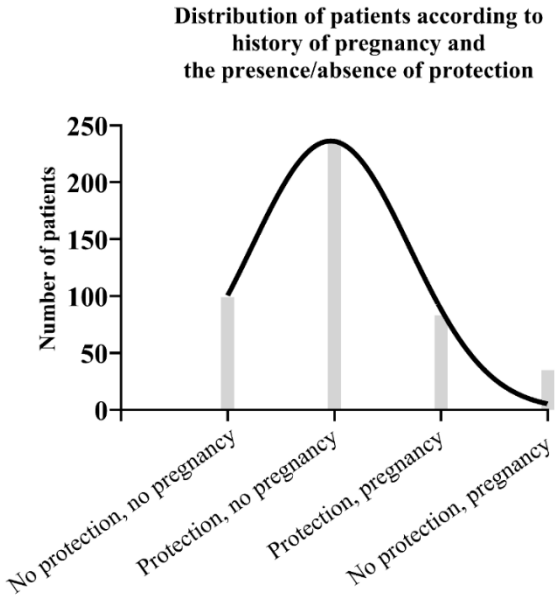

Figure 4. The distribution of patients with previous pregnancy in history and the presence and absence of protection

5. Conclusions

Our experiments focused on the following questions:

1) The sistematic summarize information based on the literature data regarding the target populations, evidence-based modern methods, effectiveness, and practical application of emergency contraception in order to reduce the occurrence of unintended pregnancies

Emergency contraception is designed for individuals who have had unprotected sexual intercourse, encountered contraceptive mishaps, or found themselves in situations where regular birth control was not utilized. Based on the 23 studies included in the literature research, the most frequently used method is the pill containing levonorgestrel, which is also confirmed by Hungarian data. In addition to LNG, UPA is also used as an emergency contraceptive in Hungary, while mifepristone and the Copper-IUD are also used in international practice. It is important to note that the most commonly used emergency contraceptive worldwide is the LNG-containing pill, however, the copper IUD has been shown to be more than 99% effective in preventing pregnancy. Regarding their side effects, there is no significant difference between the different methods, the most common side effects are nausea, headache and lower abdominal pain.

2) The elucidation and comprehension the factors that promote women to seek emergency contraception immediately after intercourse

Women who possess comprehensive knowledge regarding emergency contraception and its accessibility are more inclined to promptly seek it following unprotected intercourse. Being aware of the time-sensitive nature of emergency contraception

and its effectiveness can motivate women to take immediate action. Women who have encountered contraceptive failures, like condom rupture, experienced unintended pregnancies, or have previous experiences with emergency contraception are more likely to promptly seek it in future instances of unprotected intercourse. Establishing a supportive and open line of communication with sexual partners can have a positive influence on a woman's determination to seek emergency contraception promptly. Partner encouragement to prioritize reproductive health and overall well-being can play a substantial role in this decision-making process.
Individuals who used condoms as a contraceptive method showed a significantly shorter time interval before seeking emergency contraception compared to those who did not use any form of protection or used alternative protective methods. Furthermore, patients with a prior history of pregnancy exhibited a notably reduced elapsed time before seeking emergency contraception.

6. Bibliography of the candidate's publications

Publications related to the thesis:

Keszthelyi LL, Vezér M, Török M, Cseh R, Keszthelyi A, Acs N, Varbiro S, Keszthelyi M. (2023) Emergency contraception - systematic review of the literature. Orv Hetil, In press.
IF: 0.6

Keszthelyi LL, Török M, Vezér M, Gerszi D, Gyarmathy VA, Acs N, Varbiro S, Keszthelyi M. (2023) Motivators for emergency contraception: previous pregnancy and condom rupture. Heliyon, under review.
IF: 4.0

Publications not related to the thesis:

Keszthelyi M, Leipold G, Lőczi L, Török M, Ács N, Várbíró S. (2023) [Herniated amniotic sac through uterine dehiscence at the 30th gestational week after prior laparoscopic salpingectomy]. Orv Hetil, 164: 988-992.
IF: 0.6

Keszthelyi M, Bakos M, Szabó I, Török M, Lőczi L, Madaras L, Ács N, Várbíró S. (2023) [Molar pregnancy in postmenopause]. Orv Hetil, 164: 273-277.
IF: 0.6

∑IF: 5,8