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Ectopic Pregnancy and Levonorgestrel - Only Emergency Contraception: A Systematic Review

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Abstract

Background: This study aimed at evaluating previously done studies on the proportion of ectopic pregnancies among women with a history of emergency contraception failure. Data was obtained from PubMed, Google Scholar and the Cochrane Database of Systematic Reviews.

Methods of Study Selection: This study included data from 114 studies which followed a defined population of women treated one time with emergency levonorgestrel-only contraceptive pills and whose number and location of pregnancies were ascertained.

Results: 14.3% (n = 2) of all the studies did not report any incidence of ectopic pregnancy following levonorgestrel-only emergency contraception. The majority of the reported cases of ectopic pregnancy were from studies done in China. Repeated use of levonorgestrel emergency contraception in the same menstrual cycle increased the risk of ectopic pregnancy.

Conclusion: The risk of ectopic pregnancy following emergency contraception failure rises when levonorgestrel only emergency contraception is used repeatedly in the same cycle or close to the ovulation period.

Key Words

Ectopic Pregnancy; Extra-uterine Pregnancy; Postcoital Contraception; Levonorgestrel.

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Introduction

Rationale

Ectopic pregnancy is the implantation of the blastocyst anywhere other than the endometrial lining of the uterine cavity¹. Extra-uterine pregnancy has been shown to increase the risk of mortality than vaginal delivery or induced abortion². Approximately 90% of ectopic pregnancies occur within the tubes³. Other sites of ectopic pregnancy include the ovary, abdominal cavity, intrauterine portion of the fallopian tube (cornual pregnancy)^{4,5}. The proportion of ectopic pregnancy is 1 in 150 pregnancies⁶. Ovarian pregnancy may occur as a result of rare fertilization and trapping of the ovum within the follicle just at the time of the rapture while abdominal pregnancy could result from the fertilized ovum dropping out of the fimbriated end of the tube⁷. In all these, the fertilized ovum undergoes its usual development with the formation of placental tissue, amniotic sac and fetus while the host implantation site develops decidual changes⁸.

The four major factors that predispose a woman to ectopic pregnancy are classified as mechanical and functional factors, assisted reproduction and failed contraception. This paper will major on failed contraception; especially emergency contraception. Levonorgestrel-only emergency contraception (LOEC) treatment failure has been attributed to ectopic pregnancy².

Objectives

To review mixed clinical studies among women aged between 18 to 45 years receiving either 0.75mg (double dose), 1.5mg (single dose) of levonorgestrel only emergency contraception.

To compare studies on women using LOEC versus those with no form of family planning.

To assess how many studies among women using LOEC had ectopic pregnancy as the outcome of interest.

Methodology

Eligibility Criteria

Clinical studies adopting randomized double-blind and case-studies case-control study design were selected for this review. The literature, which included women of fertile age, compared one and/or two doses of levonorgestrel taken in different regimens. Reasons for exclusion included non-English studies, literatures involving non-human models, studies which compared levonorgestrel with other emergency hormonal contraceptives and publications concerned with dosage forms other than oral tablets.

Information Sources

PubMed, Google Scholar and Mendeley databases were searched from 2000–2017 using the key terms: emergency contraception, postcoital contraceptives and levonorgestrel-only emergency contraception.

Search

Studies were checked for duplicates and relevance for review by looking at title and abstracts. Where it was not possible to exclude publications by reviewing the title or abstract, the full paper was retrieved and reviewed.

Study Selection

Decisions for trials to be included were independently made by two reviewers. The references of the retrieved studies were searched for further studies. The selected studies were assessed for use of levonorgestrel only emergency contraception and the occurrence of ectopic pregnancy as an outcome.

Data Collection Process

The data collected was keyed into a data collection table containing: the authors, country where the study was conducted, the population characteristics such as age range, study title, design and outcome (whether or not ectopic pregnancy was reported).

Data Items

The first two authors independently reviewed the search results for studies of clinical trials or case-control study design where levonorgestrel was taken orally for contraception and whether or not there was ectopic pregnancy as an outcome.

Summary Measures

The principal summary measures were significant associations, risk ratios and mean differences.

Risk of Bias Across Studies

This was assessed using the Cochrane Collaboration risk of bias assessment tool. RevMan was used to plot the risk of bias. Selection bias was assessed by conducting sequence generation and allocation concealment.

Outcome Measures

Pregnancy rates, percent of pregnancies prevented, side-effects and occurrence of ectopic pregnancy were assessed as the study outcomes. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) criteria for reporting systematic reviews of studies was used to evaluate healthcare interventions as a quality appraisal tool.

Results

Study Selection: 107 relevant studies (as shown in the study selection flow diagram - Figure 1) were identified through database searches and an additional 35 records were identified. There were 114 records after the duplicates were removed. 114 records were screened and 62 records were excluded, leaving 52 full texts for eligibility assessment of which 14 were included. The excluded, 38 studies had either incomplete information on the drug regimen, number of pregnancies, the duration of data collection or compared levonorgestrel only emergency contraceptives with other compounds and therefore those ten studies were omitted from this review. Discrepancies were resolved by discussion and consultation with other reviewers including clinicians if needed.

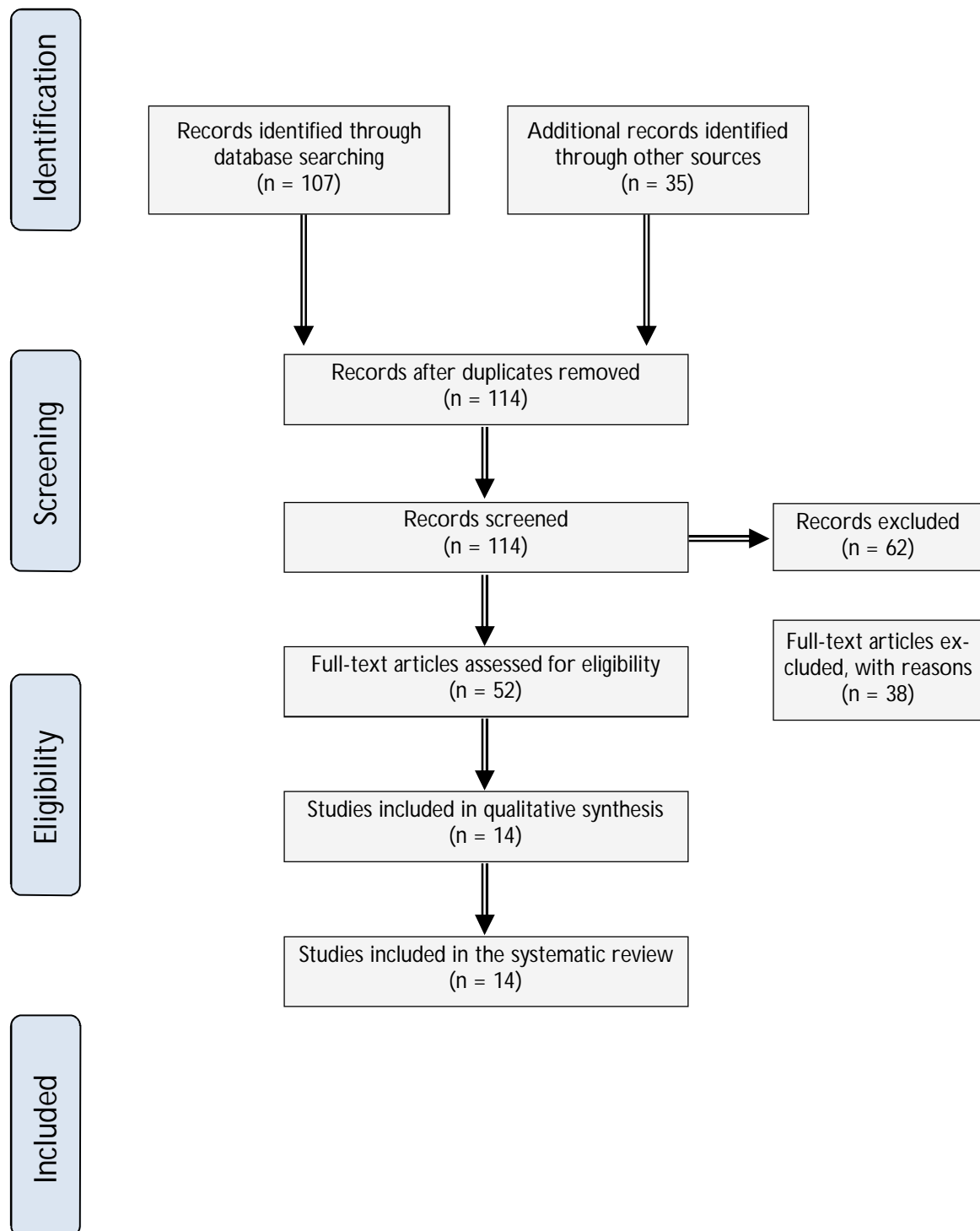


Figure 1: PRISMA 2009 Flow Diagram

Table 1: Study Characteristics

The occurrence of ectopic pregnancy following emergency contraception failure has been found to occur most commonly in China and parts of South East Asia, Africa and Latin America. In this study, the same pattern was observed.

Authors (Year)	Country	Population Characteristics		Study Title, Design and Outcome	
		No. of Subjects	Age (Years)	Study Title and Design	Outcome Ectopic Pregnancy (Yes/No)
Q.J. Chen, W.P. Xiang, D.K. Zhang, R.P. Wang, Y.F. Luo, J.Z. Kang, & L.N. Cheng (2011)	China	2445	15–48	Efficacy and safety of a levonorgestrel enteric-coated tablet as an over-the-counter drug for emergency contraception: a Phase IV clinical trial(9).	No
Suk Wai Ngai, Susan Fan, Shiqin Li, Linan Cheng, Juhong Ding, Xiaoping Jing, Ernest Hung, Yu Ng & Pak Chung Ho1 (2005)	China	2071	27 (mean)	A randomized trial to compare 24 h versus 12 h double dose regimen of levonorgestrel for emergency contraception(10) (Clinical Trial 1997 and 2003)	No
Hung-Hung Lin1, Ming-Chao Huang, Chen-Ju Lin, Chih-Ping Chen	Taiwan	1	29	Ectopic Pregnancy with oral contraceptive (11)(Case-study; letter to the editor)	Yes
Kelly Cleland, Elizabeth Raymond, James Trussell, Linan Cheng & Haoping Zhu (2010).	China	137 (studies)		Ectopic Pregnancy and Emergency Contraceptive Pills: A Systematic Review(12)	Yes
Pedro Paulo Pereira, Fábio Roberto Cabar, Luciana Cristina Pasquini Raiza, Maria Teresa Roncaglia, and Marcelo Zugaib (2005)	Brazil	2	30.5 (mean)	Emergency Contraception and Ectopic Pregnancy: Report of 2 Cases (13)	Yes
Zhuomin, Zhang Liju, Weng, Zhiyan, Zhang, Xunxun, Jin Xiaoping, Jing Liying, Zhang, Shizhu, Lian Yibing, Cui (1994)	China	1,420		An epidemiological study on the relationship of ectopic pregnancy and the use of contraceptives in Beijing(14).	Yes
Jian Zhang, Cheng Li, Wei-Hong Zhao, Xiaowei Xi, Shu-Jun Cao, Hua Ping, Guo-Juan Qin, Linan Cheng & He-Feng Huang (2015).	China	7,246		Association between levonorgestrel emergency contraception and the risk of ectopic pregnancy: a multicenter case-control study (15)	Yes
Gabriela Noé, Horacio B.Croxatto, Ana María Salvatierra, Verónica Reyes, Claudio Villarroel, Carla Muñoz, Gabriela Morales, Anita Retamales. (2009)	Chile	388		Contraceptive efficacy of emergency contraception with levonorgestrel given before or after ovulation (16)	Yes
Cheng Li, Chun-Xia Meng, Lu-Lu Sun, Wei-Hong Zhao, Mei Zhang, Jian Zhang and Linan Cheng (2015)	China	79	31.94 ± 0.59	Reduced prevalence of chronic tubal inflammation in tubal pregnancies after levonorgestrel emergency contraception failure (17)	Yes
Cheng Li, Wei-Hong Zhao, Qian Zhu, Shu-Jun Cao, Hua Ping, Xiaowei Xi, Guo-Juan Qin, Ming-Xing Yan, Duo Zhang, Jun Qiu and Jian Zhang	China	2411		Risk factors for ectopic pregnancy: a multicenter case-control study (18)	Yes
Cheng Li, Wei-Hong Zhao, Chun-Xia Meng, Hua Ping, Guo-Juan Qin, Shu-Jun Cao, Xiaowei Xi, Qian Zhu1, Xiao-Cui Li, Jian Zhang (2014)	China	7246		Contraceptive Use and the Risk of Ectopic Pregnancy: A Multi-Center Case-Control Study (19)	Yes
Duo Zhang, Ming-Xing Yan, Jue Ma, Wei Xia, Rui-Hong Xue, Jing Sun and Jian Zhang (2016)	China	300	20->40	Association between knowledge about levonorgestrel emergency contraception and the risk of ectopic pregnancy following levonorgestrel emergency contraception failure: a comparative survey (20)	Yes
Jian Zhang, Cheng Li, Wei-Hong Zhao, Xiaowei Xi, Shu-Jun Cao, Hua Ping, Guo-Juan Qin, Linan Cheng & He-Feng Huang (2015)	China	2411		Association between levonorgestrel emergency contraception and the risk of ectopic pregnancy: a multicenter case-control study (15)	Yes
Laura Fabunmi and Nigel Perks (2002)	United Kingdom	1	38	Caesarean section scar ectopic pregnancy following postcoital contraception: Case Study(21)	Yes

Discussion

Summary of Evidence:

In this review, 14.3% (n = 2) of all the studies did not report any incidence of ectopic pregnancy following levonorgestrel-only emergency contraception. In a phase IV post-marketing study of a new enteric coated levonorgestrel-only emergency contraceptive (E-LNG ECP) as an over the counter medication in China⁹, it was found that the efficacy rate of E-LNG ECP was 95.3% with a failure rate of only 0.2%. This could be attributed to the fact that majority (82.7%) of all the study participants took their first dose within 24 hours after their unprotected sexual intercourse. Previous studies^{22,23} have attributed increased odds of pregnancy following emergency contraception failure by 50% when the first dose is delayed by 12 hours. This study did not find any incidence of ectopic pregnancy as an adverse event. The only complaints reported by 7.1% (n = 165) of all participants were nausea, vaginal bleeding, headache, xerostomia, vomiting, transient chest distress, lower abdominal pain, anorexia, fatigue and dizziness. The study noted a reduced incidence of nausea (4.2%; n = 108) due to the enteric coated nature of the emergency contraceptive pill compared to other randomized controlled trials done on non-enteric coated emergency contraceptive pills^{24,25}. A second study conducted in Hong Kong determined that 0.75 mg levonorgestrel given 24 hour apart is as effective as the 12-hour regimen for emergency post-coital contraception up to 120 hour after unprotected intercourse¹⁰. The authors suggested that the long half-life of levonorgestrel and the resultant maintenance of high plasma concentrations probably explain why the 24 hour dosing interval is also effective¹⁰. However, the pregnancy rates following emergency contraception failure were 1.9% (95% CI: 1.2–2.9) in the 24-hour regimen, 2.0% (95% CI: 1.2–3.0) in the 12-hour regimen group and 2.7% (P > 0.05) in the 72-hour regimen group. These results were consistent with the results among Chinese women in a World Health Organization commissioned study²⁴. Further acts of unprotected coitus increased the likelihood of pregnancy significantly (p = 0.003) with an odds ratio of 3.62 (95% CI: 1.49–8.81) in the 12-hour regimen group and odds of 0.88 (95% CI: 0.29–2.65) in the 24-hour regimen group.

Although the literature search focused on studies conducted globally, majority of the studies were from Asia. This could be attributed to the great uptake of emergency contraception alongside other contraception options due to the one child policy in

China at the time the studies were being conducted. This does not exclude the fact that in the event of emergency contraception failure or repeat use of emergency contraception in the same cycle increases the likelihood (Adjusted OR [AOR] 2.49, 95%CI: 1.00–6.19) of the subsequent pregnancy being ectopic¹⁵. In the third Chinese study¹⁵, it was determined that previous use of LOEC was not correlated with ectopic pregnancy and that LOEC reduced the risk for intrauterine pregnancy (AOR 0.20, 95%CI: 0.14–0.27), but did not increase the risk for ectopic pregnancy (AOR 1.04, 95%CI: 0.76–1.42). The risk of ectopic pregnancy increased among women who further had unprotected sexual intercourse following LOEC use (AOR 2.35, 95% CI: 1.17–4.71). The authors recommended a better understanding of the risk of ectopic pregnancy following LOEC failure could optimize LOEC use and thus reduce the risk of ectopic pregnancy.

Lastly, the ground breaking study in ectopic pregnancy following LOEC use was a case study in the United Kingdom²¹. This was a multiparous woman who had a failed progestogen-only emergency contraception. Another case study from Brazil¹³ reported ectopic pregnancy among two women who had correctly used LOEC following unprotected sexual intercourse. The authors argued that the use of emergency contraception close to the ovulation period lowers the chance of modifying ovulatory function. This could explain higher contraception failure rates observed after use during this period, and could increase the risk of ectopic pregnancy¹³.

Limitations:

We could not access all studies on ectopic pregnancy following emergency contraception failure from other countries and jurisdiction.

Conclusions:

The risk of ectopic pregnancy following emergency contraception failure rises when levonorgestrel-only emergency contraception is used repeatedly in the same cycle or close to the ovulation period. More awareness campaigns should be conducted to create awareness on the proper method and timing of use. Other long term forms of family planning should be encouraged as potential users are discouraged on using emergency contraception as a routine form of family planning.

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