# ORIGINAL REPORT

# Association between knowledge about levonorgestrel emergency contraception and the risk of ectopic pregnancy following levonorgestrel emergency contraception failure: a comparative survey

Duo Zhang<sup>1,2</sup>, Ming-Xing Yan<sup>1,2</sup>, Jue Ma<sup>1,2</sup>, Wei Xia<sup>1,2</sup>, Rui-Hong Xue<sup>1,2</sup>, Jing Sun<sup>3\*</sup> and Jian Zhang<sup>1,2\*</sup>

#### ABSTRACT

Objective To study the association between knowledge about levonorgestrel emergency contraception (LNG-EC) and the risk of ectopic pregnancy (EP) following LNG-EC failure.

Methods This study included 600 women who had visited the hospital with LNG-EC failure. Of these, 300 with EP and 300 with intrauterine pregnancy (IUP) were recruited to the EP group and IUP group respectively. The participants were interviewed face-to-face using a standardized questionnaire.

Main Outcome Measures Pearson's chi-square tests and t-test were used to compare the sociodemographic characteristics, reproductive and gynecological history, surgical history, previous contraceptive experience, and answers to 10 questions concerning the knowledge about LNG-EC.

Results Those who gave incorrect answers to the question regarding the basic mechanism and specific method of levonorgestrel emergency contraceptive pills (LNG-ECPs) were at a higher risk of EP after LNG-EC failure. Women who did not strictly follow instructions or advice from healthcare professionals were more likely to subsequently experience EP ( $p < 10^{-4}$ ). Women with LNG-EC failure reported friends/peers, TV, and Internet as the main sources of information. No difference was observed with regard to the sources of knowledge on LNG-EC (p = 0.07).

**Conclusions** The results illustrate the importance of strictly following the doctor's guidance or drug instructions when using LNG-ECPs. The media should be used to disseminate information about responsible EC, and pharmacy staff should receive regular educational training sessions in this regard. © 2016 The Authors. Pharmacoepidemiology and Drug Safety published by John Wiley & Sons Ltd.

KEY WORDS—knowledge; levonorgestrel; emergency contraception; ectopic pregnancy; contraceptive failure; pharmacoepidemiology

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## INTRODUCTION

Postcoital contraception or emergency contraception (EC) refers to the use of drugs or other interventions to prevent unwanted pregnancy after unprotected sexual intercourse.<sup>1,2</sup> EC differs from long-term contraceptive measures, and is an extremely effective back-up method in the instance of non-use or failure of regular contraceptives.<sup>2</sup> Currently, mifepristone and levonorgestrel (LNG) are the available hormonal

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 $<sup>^1</sup>$ Department of Obstetrics and Gynecology, International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai

Jiaotong University, Shanghai, China <sup>2</sup>Institute of Embryo-Fetal Original Adult Disease Affiliated to School of Medicine, Shanghai Jiaotong University, Shanghai, China <sup>3</sup> Department of Obstetrics and Gynecology, Shanghai First Maternity and Infant Hospital, Tong Ji University School of Medicine, Shanghai,

<sup>\*</sup>Correspondence to: J. Zhang, Department of Obstetrics and Gynecology, International Peace Maternity and Child Health Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200030, China. E-mail: zhangjian\_ipmch@sjtu.edu.cn

J. Sun, Department of Obstetrics and Gynecology, Shanghai First Materrnity and Infant Hospital, Tong Ji University School of Medicine, Shanghai 200040, China. E-mail: sunjing61867@126.com

<sup>&</sup>lt;sup>†</sup>A statement about prior postings and presentations: This paper has not been submitted to any other journal for publication.

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EC drugs in Mainland China. Mifepristone can only be obtained with a prescription, thereby limiting its use in China. LNG in a single dose of 1.5 mg or two doses of 0.75 mg taken 12 h apart, which has superior efficacy and fewer adverse effects than the Yuzpe regimen, is the most widely used golden standard EC regimen in China.<sup>3,4</sup> Both dosage regimens have equal efficiency and safety, and have been reported to prevent unwanted pregnancies in 74–93% of the cases.<sup>3,5</sup> In 1998, levonorgestrel emergency contraception (LNG-EC) was approved as an over-the-counter drug sold in China; currently, Chinese women prefer to directly purchase this drug from pharmacies than obtain EC from doctors.<sup>6</sup> As LNG is extremely convenient, relatively safe, and well-tolerated, it has now become the first line of hormonal EC among women of childbearing age. A sales analysis from the two largest Chinese pharmaceutical companies that manufacture and sell levonorgestrel emergency contraceptive pills (LNG-ECPs) revealed that in the city of Shanghai, 790000 boxes containing either 2 1.5-mg or 4 0.75-mg pills were sold in 2012 alone (Cheng, personal data).

However, with the widespread use of LNG-EC, many concerns have been raised regarding the risk of ectopic pregnancy (EP) following LNG-EC failure. Not only is EP a leading cause of maternal morbidity and mortality worldwide but it is also a risk factor for recurrent EP and impaired fertility. 11,12 Our recent large-sample multicenter study reported a sharp increase in the risk of EP following LNG-EC failure compared to non-users (adjusted odds ratio [AOR] = 5.29, 95% confidence interval [CI] = 4.07–6.87). Moreover, LNG-EC misuse has been demonstrated to be correlated with a high risk of EP following LNG-EC failure. 13

Westley et al. indicated that despite the growing use of emergency contraceptive pills (ECPs), proper information posed an important barrier to the desired impact on the unintended pregnancy rate.14 In another study, lack of awareness and misunderstanding about EC methods were shown to be the main obstacle to effective EC use. 15 In general, the desired effect of EC can be produced only by correct use, which is closely correlated with knowledge about EC. Thus far, no studies have investigated the association between high risk for EP following LNG-EC failure and knowledge of LNG-EC. Therefore, we conducted a comparative survey among women with LNG-EC failure to determine whether a correlation exists between the EP incidence following LNG-EC and knowledge of LNG-EC.

## MATERIALS AND METHODS

#### Ethics statement

This comparative survey was approved by the Institutional Review Board at the International Peace Maternity and Child Health Hospital, Shanghai, China. Written informed consents were obtained from all the subjects before recruitment. The participants were told that they could refuse the interview and withdraw from the study at any time, and that all information would be kept strictly confidential.

# **Participants**

Women who presented at our hospital from March 2010 to April 2013 with a diagnosis of EP according to the unified diagnostic criteria (ACOG Practice Bulletin)<sup>16</sup> were considered for participation in this comparative survey. Among these, women who had taken LNG-EC since their last menstrual period were defined as having EP following LNG-EC failure and were recruited to the EP group (EP following LNG-EC failure).<sup>17</sup> During the same period, patients who visited the pre-abortion or early pregnancy clinics with intrauterine pregnancy (IUP) who had taken LNG-EC since the last menstrual period were recruited to the IUP group (IUP following LNG-EC failure). Patients in the IUP group were matched in age (±5 years), marital status, and gestational weeks (±7 days) at a ratio of 1:1 using their visiting numbers.

# Data and sample collection

After informed consents were obtained, the study participants were interviewed in person using a structured questionnaire covering sociodemographic characteristics (age, marital status, birth place, education attainment, occupation, individual annual income, and smoking status), reproductive and gynecological history (number of previous abortions, parity, previous EP, and results of the serum chlamydia trachomatis [CT] IgG test), surgical history (previous cesarean section, previous adnexal surgery, and appendectomy), previous contraceptive experience (OCPs, IUDs, ECPs, and condoms), key point of LNG-EC, and sources of knowledge about LNG-EC. Previous and current use of a certain contraceptive method was defined in line with the definitions in one of our previous studies.<sup>17</sup> To assess the actual knowledge about LNG-EC among women with LNG-EC failure, an additional questionnaire consisting of 10 questions was specially designed. The questionnaire covered the mechanism of action, time frame, specific methods,

complications of LNG-EC when used in combination with other treatments and drug interactions. The participants were required to answer each question using Yes or No. To ensure a high completion rate and accuracy, the questionnaires were filled out by female researchers during the interview. In addition, blood samples were collected from each participant to test for serum CT IgG antibody using ELISA (Beijing Biosynthesis Biotechnology, China).

## Statistical analysis

Pearson's chi-square tests and t-test were used to detect the difference between the EP group and IUP group in terms of the sociodemographic characteristics [age (20–29, 30–39, or  $\geq$ 40 years); marital status (married or unmarried); educational level (primary school or lower primary, middle school, high school, or university or above); occupation (employed, selfemployed, or unemployed); smoking status (nonsmoker, occasional smoker, or regular smoker)], history of reproduction [number of previous abortions  $(0, 1, 2, \text{ or } \ge 3)$ ; parity  $(0, 1, \text{ or } \ge 2)$ ], gynecology [previous EP (no or yes); serum CT IgG test (negative or positive)], surgery [previous cesarean section (no or yes); previous adnexal surgery (no or yes); previous appendectomy (no or yes)], previous contraceptive experience [OCPs (no or yes); IUD (no or yes), ECPs (no or yes), and condoms (no or yes)] and participants' answer to each question. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC). The p values were estimated by two-sided tests, and the results were considered statistically significant when p < 0.05.

## **RESULTS**

A total of 310 EP patients and 317 IUP women following LNG-EC failure were included in this study. After eliminating 27 participants who declined entry or had incomplete information (10 in the EP group and 17 in the IUP group), 600 subjects (300 in the EP group and 300 in the IUP group) remained in the present study with a response rate of 95.69% (recruitment profile shown in Figure 1).

# Sociodemographic characteristics

Table 1 lists the sociodemographic characteristics of the two groups. Significant differences were observed between the two groups in terms of their occupation  $(p < 10^{-4})$  and educational attainment (p = 0.02). Apart from this, there were no statistical differences in the age, marital status, birth place, personal annual income, and smoking status between the two groups. The age of women (year; mean  $\pm$  SD) was 27.05  $\pm$ 4.73 in the EP group and 27.50  $\pm$ 4.94 in the IUP group (data not shown in table). In addition, the gestational week (week; mean  $\pm$  SD) of EP and IUP group were 6.78  $\pm$ 1.40 and 6.88  $\pm$ 1.80 respectively, and no significant difference was observed (p = 0.39) (data not shown in table).

# Reproductive, gynecological, surgical, and contraceptive history

Table 2 summarizes the difference in the reproductive, gynecological, surgical history, and previous contraceptive experience of these women between two groups. No significant differences were found in the number of previous abortions; previous EP; serum

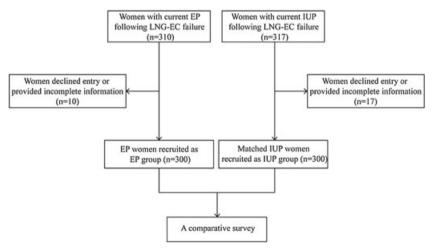


Figure 1. Recruitment profile of subjects included in this study

Table 1. Sociodemographic characteristics

| Variables                    | EP following LNG-E | EC failure $(N = 300)$ | IUP following LNG-EC failure (N = 300) |       | p Value     |
|------------------------------|--------------------|------------------------|--|-------|-------------|
|                              | n*                 | (%)                    | n*                                     | (%)   |             |
| Age (years)                  |                    |                        |  |       | 0.18        |
| 20–29                        | 203                | 67.67                  | 183                                    | 61.00 |             |
| 30-39                        | 94                 | 31.33                  | 111                                    | 37.00 |             |
| ≥40                          | 3                  | 1.00                   | 6                                      | 2.00  |             |
| Marital status               |                    |                        |  |       | 0.10        |
| Married                      | 185                | 61.87                  | 205                                    | 68.33 |             |
| Unmarried                    | 114                | 38.13                  | 95                                     | 31.67 |             |
| Birth place                  |                    |                        |  |       | 0.47        |
| Shanghai                     | 216                | 72.00                  | 208                                    | 69.33 |             |
| Out of Shanghai              | 84                 | 28.00                  | 92                                     | 30.67 |             |
| Educational attainment       |                    |                        |  |       | 0.02        |
| Primary school or lower      | 72                 | 24.00                  | 47                                     | 15.67 |             |
| Middle school                | 33                 | 11.00                  | 29                                     | 9.67  |             |
| High school                  | 48                 | 16.00                  | 41                                     | 13.67 |             |
| University or above          | 147                | 49.00                  | 183                                    | 61.00 |             |
| Occupation                   |                    |                        |  |       | $< 10^{-4}$ |
| Employed                     | 211                | 70.33                  | 251                                    | 83.67 |             |
| Self-employed                | 43                 | 14.33                  | 14                                     | 4.67  |             |
| Unemployed                   | 46                 | 15.33                  | 35                                     | 11.67 |             |
| Individual annual income (¥) |                    |                        |  |       | 0.13        |
| < 50 000                     | 145                | 48.33                  | 125                                    | 41.67 |             |
| 50 000-100 000               | 101                | 33.67                  | 103                                    | 34.33 |             |
| >100 000                     | 54                 | 18.00                  | 72                                     | 24.00 |             |
| Smoking status <sup>†</sup>  |                    |                        |  |       | 0.18        |
| Non-smoker                   | 283                | 94.33                  | 274                                    | 91.95 |             |
| Occasional smoker            | 9                  | 3.00                   | 18                                     | 6.04  |             |
| Regular smoker               | 8                  | 2.67                   | 6                                      | 2.01  |             |

Note: EP = ectopic pregnancy, LNG-EC = levonorgestrel emergency contraception, IUP = intrauterine pregnancy.

CT IgG test; surgical history including cesarean section, adnexal surgery, and appendectomy; and previous use of OCPs and ECPs. The parity differed significantly between both the groups (p=0.01). Compared with the IUP group, previous IUD use was more common in the EP group (p=0.03). Contrarily, the proportion of women who previously used condoms as contraception was significantly greater in IUP group than the EP group (p<10<sup>-4</sup>).

# Knowledge about LNG-EC

The present study focuses on women who became pregnant following LNG-EC failure in the current cycle; therefore, all the participants replied "Yes" to the question, "Have you ever heard of LNG-EC?" (data not shown). Table 3 presents the results of 10 closed questions. Women who mistakenly assumed that LNG-EC was an abortion pill were more likely to experience EP following LNG-EC failure than women who did not have this misconception (p=0.04);

62.37% and 34.35% of women in EP group and IUP group, respectively, were unaware that further unprotected sexual intercourse after use of LNG-EC should be avoided  $(p < 10^{-4})$ . Women who agreed with the repeated use of LNG-ECPs in the same cycle were more likely to suffer EP after LNG-EC failure  $(p < 10^{-4})$ . Compared with women who took LNG-ECPs strictly according to a healthcare professional's advice or according to package instructions, those who did not strictly follow guidelines and instructions were significantly more likely to experience EP following LNG-EC failure ( $p < 10^{-4}$ ). However, ignorance of the treatment window posed no risk for EP (p=0.14). Unfamiliarity with possibility of EP as a consequence of LNG-EC failure (p = 0.92), complications of ECPs including abnormal uterine bleeding (p=0.81), menstrual cycle changes (p=0.89), and drug interactions (p=0.10) had no association with the occurrence of EP following LNG-EC. Women who did not know how to deal with vomiting within 2h after LNG-ECPs use had higher risk for EP  $(p < 10^{-2}).$ 

<sup>\*</sup>The sum does not necessarily equal the sample size for all variables because of missing data.

<sup>†</sup>Occasional smoker: cigarette smoking more than 4 times a week, but a day on average less than 1 cigarette. Regular smoker: cigarette smoking more than 1 cigarettes per day, continuous or accumulated 6 months.

Table 2. History of reproduction, gynecology, surgery, and contraceptive experiences

| Variables                              | EP following LNG-EC failure ( $N = 300$ ) |       | IUP following LNG-EC failure ( $N = 300$ ) |       | p Value     |
|--|---|-------|--|-------|-------------|
|  | n*  | (%)   | n*   | (%)   |             |
| Reproductive history                   |   |       |  |       |             |
| Number of previous abortions           |   |       |  |       | 0.32        |
| 0                                      | 100                                       | 34.25 | 85   | 28.33 |             |
| 1                                      | 101                                       | 34.59 | 110  | 36.67 |             |
| 2                                      | 55  | 18.84 | 56   | 18.67 |             |
|  | 36  | 12.33 | 49   | 16.33 |             |
| Parity                                 | 50  | 12.00 | ••   | 10.00 | 0.01        |
| 0                                      | 132                                       | 45.21 | 162  | 54.18 | 0.01        |
| 1                                      | 139                                       | 47.60 | 129  | 43.14 |             |
|  | 21  | 7.19  | 8  | 2.68  |             |
| Gynecologic history                    | 21  | 7.17  | o  | 2.00  |             |
| Previous EP                            |   |       |  |       | 1.00        |
| No                                     | 291                                       | 97.00 | 291  | 97.00 | 1.00        |
| Yes                                    | 9   | 3.00  | 9  | 3.00  |             |
|  | 9   | 3.00  | 9  | 3.00  | 0.40        |
| Serum CT IgG test                      | 264                                       | 89.80 | 261  | 87.58 | 0.40        |
| Negative                               | 30  |       |  |       |             |
| Positive                               | 30  | 10.20 | 37   | 12.42 |             |
| Surgical history                       |   |       |  |       | 0.42        |
| Previous cesarean section <sup>†</sup> | 0.5                                       | 52.12 | 70   | 57.66 | 0.43        |
| No                                     | 85<br>7.5                                 | 53.13 | 79<br>50                                   | 57.66 |             |
| Yes                                    | 75  | 46.88 | 58   | 42.34 | 0.60        |
| Previous adnexal surgery               |   |       |  |       | 0.69        |
| No                                     | 287                                       | 95.67 | 287  | 96.31 |             |
| Yes                                    | 13  | 4.33  | 11   | 3.69  |             |
| Previous appendectomy                  |   |       |  |       | 0.54        |
| No                                     | 285                                       | 95.32 | 289  | 96.33 |             |
| Yes                                    | 14  | 4.68  | 11   | 3.67  |             |
| Previous contraceptive experiences     | <b>3</b>                                  |       |  |       |             |
| OCPs                                   |   |       |  |       | 0.08        |
| No                                     | 287                                       | 95.99 | 278  | 92.67 |             |
| Yes                                    | 12  | 4.01  | 22   | 7.33  |             |
| IUDs                                   |   |       |  |       | 0.03        |
| No                                     | 270                                       | 90.30 | 285  | 95.00 |             |
| Yes                                    | 29  | 9.70  | 15   | 5.00  |             |
| ECPs                                   |   |       |  |       | 0.07        |
| No                                     | 24  | 8.14  | 38   | 12.71 |             |
| Yes                                    | 271                                       | 91.86 | 261  | 87.29 |             |
| Condom                                 |   |       |  |       | $< 10^{-4}$ |
| No                                     | 133                                       | 44.63 | 71   | 23.67 |             |
| Yes                                    | 165                                       | 55.37 | 229  | 76.33 |             |

Note: EP = ectopic pregnancy, IUP = intrauterine pregnancy, LNG-EC = levonorgestrel emergency contraception, CT = chlamydia trachomatis, OCPs = oral contraceptive pills, IUDs = intrauterine devices, ECPs = emergency contraceptive pills.

Sources of knowledge about emergency contraception

In the EP group, a similar number of women reported acquiring knowledge about LNG-EC from friends/peers and TV (68/300, 22.67%) and the Internet (56, 18.67%; Table 4). In the IUP group, the most common source of LNG-EC was friends/peers (30.46%) followed by the Internet (18.21%) and TV (15.56%). Notably, women from both the groups were least likely to learn about LNG-EC from medical staff (EP group: 2.67% and IUP group: 2.65%). In contrast, a higher proportion of women obtained knowledge of LNG-EC from retail pharmacy staff (EP group:

17.00% and IUP group: 9.93%). There was no significant difference in the distribution of sources (p = 0.07).

## DISCUSSION

In this study, we found that unaware of the mechanism and proper use of LNG-ECPs and non-compliance with medicine instruction or doctors' advice may contribute to the occurrence of EP following LNG-EC failure. Among women with LNG-EC failure, "friends/peers", "TV", and "Internet" are the main sources of information of LNG-EC.

<sup>\*</sup>The sum does not necessarily equal the sample size for all variables because of missing data.

<sup>&</sup>lt;sup>†</sup>The number of women having delivered a child (160 women in the EP group and 137 women in the IUP group) was used as the denomintor to calculate the percentage.

Table 3. Knowledge about LNG-EC

| Questions  | EP following (N= | EP following LNG-EC failure $(N=300)$ | IUP following $(N=$ | IUP following LNG-EC failure<br>(N=300) | p<br>Value  |
|--|------------------|---------------------------------------|---------------------|---|-------------|
|  | $n^{\dagger}$    | (%)                                   | $n^{\dagger}$       | (%)                                     |             |
| LNG-ECPs are not another term for "abortion pills".  |                  |                                       |                     |   | 0.04        |
| Yes*   | 281              | 95.25                                 | 295                 | 98.33                                   |             |
| No No  | 14               | 4.75                                  | 5                   | 1.67                                    | ,           |
| LNG-ECPs should be taken within 72 h and up to 120 h after unprotected sexual intercourse.                       | 6                | 10                                    | O S                 | 66.70                                   | 0.14        |
| res*<br>No   | 240<br>53        | 81.91<br>18.09                        | 239<br>41           | 86.33<br>13.67                          |             |
| Further act of unprotected sexual intercourse after use of LNG-ECPs in the same menstrual cycle is inapproriate. |                  |                                       |                     |   | $< 10^{-4}$ |
| Yes*   | 111              | 37.63                                 | 193                 | 65.65                                   |             |
| No<br>   | 184              | 62.37                                 | 101                 | 34.35                                   |             |
| LNG-ECPs cannot be used repeatedly in the same menstrual cycle.  | ,                | ;                                     | ļ                   | ;                                       | 4           |
| Yes*   | 224              | 75.93                                 | 276                 | 93.24                                   | <10_1       |
| °Z.  | 71               | 24.07                                 | 20                  | 92.9                                    |             |
| EP may occur as a result of LNG-EC failure.  |                  |                                       |                     |   |             |
| Yes*   | 179              | 60.27                                 | 182                 | 29.09                                   | 0.92        |
|  | 118              | 39.73                                 | 118                 | 39.33                                   |             |
| Did you take LNG-ECPs this time in strict accordance with the drug instruction or doctors' advice?               |                  |                                       |                     |   |             |
| Yes  | 115              | 38.46                                 | 192                 | 64.00                                   | <10_4       |
| No   | 184              | 61.54                                 | 108                 | 36.00                                   |             |
| Abnormal uterine bleeding may occur after the use of LNG-ECPs.   |                  |                                       |                     |   |             |
| Yes*   | 133              | 44.33                                 | 130                 | 43.33                                   | 0.81        |
| No   | 167              | 55.67                                 | 170                 | 26.67                                   |             |
| Taking LNG-ECPs may cause changes in your menstrual cycle.   | Ş                | i                                     | Ş                   | ţ                                       | 0           |
| Yes*   | 161              | 54.21                                 | 161                 | 23.67                                   | 0.89        |
| No   | 136              | 45.79                                 | 139                 | 46.33                                   |             |
| If you vomit within 2 h after the use of LNG-ECPs, you should take another pill immediately. $x_{\infty,*}$      | 9                | 31 70                                 | 117                 | 00.00                                   | 710-2       |
| I cs.  | 6/               | 27.13                                 | 11/                 | 39.39                                   | <10         |
| o.X  | 212              | 72.85                                 | 180                 | 60.61                                   |             |
| LNG-ECPs may have drug interaction with other drugs.   | ì                |                                       | Î                   |   |             |
| Yes*   | 28               | 22.14                                 | 6/                  | 28.21                                   | 0.10        |
| No   | 204              | 77.86                                 | 201                 | 71.79                                   |             |
|  |                  |                                       |                     |   |             |

Note: LNG-EC= levonorgestrel emergency contraception, EP = ectopic pregnancy, IUP = intrauterine pregnancy, LNG-ECPs = levonorgestrel emergency contraceptive pills, OR = odds ratio, CI = confidence interval, AOR = adjusted odds ratio.

†The sum does not necessarily equal the sample size for all variables because of missing data.

\*Indicates the correct answer.

Table 4. Sources of knowledge about LNG-EC

| Variables                                | EP following LNG-EC failure ( $n = 300$ ) |       | IUP following LNG-EC failure ( $n = 300$ ) |       | p Value |
|--|---|-------|--|-------|---------|
|  | n*  | (%)   | $n^*$                                      | (%)   |         |
| Where did you mainly learn about LNG-EC? |   |       |  |       | 0.07    |
| Internet                                 | 56  | 18.67 | 54   | 18.21 |         |
| TV                                       | 68  | 22.67 | 47   | 15.56 |         |
| Print                                    | 17  | 5.67  | 32   | 10.60 |         |
| Friends/Peers                            | 68  | 22.67 | 91   | 30.46 |         |
| Family                                   | 32  | 10.67 | 38   | 12.58 |         |
| Medical staff                            | 8   | 2.67  | 8  | 2.65  |         |
| Retail pharmacy staff                    | 51  | 17.00 | 30   | 9.93  |         |

Note: LNG-EC = levonorgestrel emergency contraception, EP = ectopic pregnancy, IUP = intrauterine pregnancy, OR = odds ratio, CI = confidence interval. \*The sum does not necessarily equal the sample size for all variables because of missing data.

Despite the increasing and widespread use of ECPs in many countries, it does not appear to reduce the rate of unintended pregnancy as desired. 14,18 Wang pointed out that the prevalence, reliability, and continuity of contraceptive use are critical for effective contraception, and particularly, the role of contraceptive failure as a fertility determinant has become increasingly highlighted. <sup>19</sup> In particular, unlike other contraceptives, there are many requirements for taking hormonal EC such as the dose, time frame, time between coitus and administration, action after pill use, and solutions for relevant complications. The efficacy of LNG-ECPs depends mostly on users' discipline and control; thus, the failure rate is high. 19 One of our previous studies indicated that the main reasons for the continuing cases of EP following LNG-EC failure are the easy accessibility and wide marketing of LNG-EC, and the use of LNG-EC without following drug instructions. 13 Apart from the lack of awareness of EC, correct use often remains low in places where people are familiar with ECPs, and this is attributed to the poor knowledge on fertility, contraception, and pregnancy risk.<sup>14</sup> To our knowledge, this is the first study concerning the association between knowledge of LNG-EC and the risk of EP following LNG-EC failure.

We demonstrated that women who were unaware of the mechanism of ECPs as inhibiting or delaying ovulation rather than inducing abortion were at a high risk of EP following LNG-EC failure. Wrong answers to this basic question reflect the terribly poor general knowledge about LNG-EC. Improper use of ECPs as a result of lack of knowledge, including repeated use of ECPs and further unprotected intercourse within the same cycle and no use of another pill as a remedial measure for vomiting may not only lead to LNG-EC failure but also increase the risk of EP following LNG-EC failure. LNG is a synthetic progestin

analogue that is a highly efficient postcoital contraceptive, and it functions by interrupting follicular development and consequently delaying or inhibiting ovulation.<sup>21</sup> Moreover, it affects the human fallopian tube by reducing smooth muscle motility and cilia beat,<sup>22,23</sup> and a reduction of tubal activity was considered as a main mechanism of embryo-tubal retention and implantation.<sup>24</sup> When taking LNG-ECPs repeatedly following fertilization, the zygote is more likely to be detained and implant in the fallopian tube. 13 If further unprotected intercourse occurs, the ovulated ovum that would linger as a result of the previous LNG-ECPs may become fertilized. 13 In fact, among 600 women recruited in our study, no one vomited within 2 h after the use of LNG-ECPs (data not shown in table). Therefore, although the number of women who know the correct remedial measure after the puke was much more in IUP group, the answers to this question may not demonstrate the relation between not taking another pill and EP but reflect EP women's poorer knowledge about LNG-EC. As demonstrated in this study, women who adhered to drug instructions or healthcare professionals' advice were found to have a lower risk of EP as a consequence of LNG-EC failure. Thus, women should use LNG-ECPs under doctors' advice or strictly comply with the package instructions. Despite the evidence showing a sharp increase in EP following LNG-EC failure, <sup>13</sup> nearly 40% of the participants did not realize the potential risks of EP associated with incorrect use of LNG-ECPs (EP and IUP groups: 39.73% and 39.33% respectively); however, ignorance of this fact was not associated with any risk of EP. From the dominant follicular selection to the rise of luteinizing hormone peak, the timeframe at which LNG-EC can be used is rather narrow and this hinders EC use. 3,25 It has been well demonstrated that the efficacy of LNG-ECPs decreases significantly with time after coitus.<sup>4</sup> A

<sup>&</sup>lt;sup>†</sup>The question is an one-choice question.

meta-analysis indicated that women taking LNG within 72 h were less likely to pregnant compared to those took LNG after 72 h (RR=0.51, 95% CI: 0.3–0.84). Despite the lack of a concrete timeframe there was no relation to EP, and as indicated here, LNG-ECPs should be used as soon as possible following unprotected intercourse because its efficacy weakens over time. <sup>27</sup>

A 2003 study in Hong Kong showed that 63.7% of Chinese women who visited birth control clinics and healthcare centers had heard about EC before and most subjects had learned about EC from the media (52.8%) and friends (23.5%).<sup>28</sup> Chen Y et al. found that in Shanghai, EC awareness among women of childbearing age was as high as 90.29%, which was much higher than the data obtained in 1989 (28.6%).29 In the UK, although 91% of women had heard about "the morning-after pill", its usage rate was as low as 7%.14 In another study, Westley et al. highlighted the role of the media in spreading misconceptions regarding EC by giving examples that BBC and an American mainstream newspaper conveying wrong messages. 14As demonstrated in the present study, TV (22.67%) and friends/peers (22.67%) are two main ways by which women in the EP group learned about EC, while women in the IUP group reported that they learned about EC from friends/peers (30.46%). Furthermore, retail pharmacy staff was a more general source of EC awareness in the case group. This finding is in accordance with findings in a previous study in which 43.06% of the customers seeking ECPs from pharmacists did not have complete information on its correct use.<sup>29</sup> It was previously found that when patients visited pharmacies to obtain ECPs, pharmacy-related barriers occurred 30% of the time, including the time for finding knowledgeable pharmacy staff. 30 We presumed that the incomplete or incorrect information supplied by pharmacists or on TV may lead to the inappropriate use of ECPs, thus increasing the chance of EP following LNG-EC failure. Therefore, consistent with other studies,<sup>31,32</sup> our findings indicate that retail pharmacy staff should be systematically educated in detail on EC and be encouraged to counsel women on EC and the correct use of ECPs. Media should be used to disseminate correct information about EC. Less than 3% (16/600) of the women in the study obtained information about EC from medical staff, which is potentially the most reliable source of information. This is mainly because of the easy accessibility of ECPs from pharmacies, and partly because of doctors lack time to discuss EC with patients, and partly because of the private nature of the subject.<sup>33</sup>

It is important to note that this study has some limitations. The coverage of our study on the knowledge of EC was not sufficiently extensive: although the participants' compliance rate was high, we did not investigate the truth of the knowledge conveyed by healthcare professionals or media. Whether the participants acted in accordance with certain correct key points remains unknown.

## CONCLUSIONS

We found that in cases of pregnancy after LNG-EC failure, women who lacked awareness on the correct usage of LNG-EC were at a high risk of EP following LNG-EC failure. Therefore, we recommend that women use LNG-EC only in strict accordance with the guidance of healthcare professionals. Various media should be used to disseminate relevant information about responsible EC, and pharmacy staff and pharmacists should receive regular educational training sessions on the subject of EC.

## **AUTHOR CONTRIBUTIONS**

Jian Zhang and Jing Sun conceived of the study and participated in its design, as well as supervised the study and critically revised the manuscript. Duo Zhang was responsible for drafting and writing the manuscript. Ming-Xing Yan and Jue Ma participated in the revising of the manuscript. Wei Xia and Rui-Hong Xue contributed to statistical analysis. All authors substantially contributed to the revision of the manuscript.

# CONFLICT OF INTEREST

The authors declare no conflict of interest.

# **KEY POINTS**

- Unawareness of its correct usage increases the risk of ectopic pregnancy after the failure of levonorgestrel emergency contraception.
- Women who did not strictly follow instructions or advice from healthcare professionals regarding levonorgestrel emergency contraception were more likely to subsequently experience ectopic pregnancy.
- The media could assist by responsibly disseminating correct information about the use of emergency contraception.

## ETHICS STATEMENT

Ethics approval was obtained from the Ethics Committee of the International Peace Maternity and Child Health Hospital.

## PATIENT CONSENT

Patient consent was obtained for inclusion in the study.

## DATA SHARING STATEMENT

All data underlying the findings described in this manuscript is fully available from the corresponding author (Prof. Jian Zhang, zhangjian\_ipmch@sjtu.edu. cn) without restriction.

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## REFERENCES

- Glasier A. Emergency postcoital contraception. N Engl J Med 1997; 337(15): 1058–1064.
- Li HW, Lo SS, Ho PC. Emergency contraception. Best Pract Res Clin Obstet Gynaecol 2014; 28(6): 835–844.
- ESHRE CapriWorkshop Group. Emergency contraception. Widely available and effective but disappointing as a public health intervention: a review. *Hum Reprod* 2015; 30(4): 751–760.
- World Health Organization. Methods for fertility regulation. Randomized controlled trial of levonorgestrel versus the Yuzpe regimen of combined oral contraceptives for emergency contraception. *Lancet* 1998; 352: 428–433.
- Von Hertzen H, Piaggio G, Ding J, et al. Low dose mifepristone and two regimens of levonorgestrel for emergency contraception: a WHO multicentre randomized trial. Lancet 2002; 360(9348): 1803–1810.
- Zhang L, Chen J, Wang Y, Ren F, Yu W, Cheng L. Pregnancy outcome after levonorgestrel-only emergency contraception failure: a prospective cohort study. *Hum Reprod* 2009; 24(7): 1605–1611.
- Kaymak O, Simşek Y, Doğanay M, Yıldız Y, Mollamahmutoğlu L. Ectopic pregnancy following levonorgestrel emergency contraception: a case report. J Turk Ger Gynecol Assoc 2010; 11(3): 168–169.

- Ghosh B, Dadhwal V, Deka D, Ramesan CK, Mittal S. Ectopic pregnancy following levonorgestrel emergency contraception: a case report. *Contraception* 2009: 79(2): 155–157.
- Jian Z, Linan C. Ectopic gestation following emergency contraception with levonorgestrel. Eur J Contracept Reprod Health Care 2003; 8(4): 225–228.
- Sarkar NN. The emergency contraceptive drug, levonorgestrel: a review of postcoital oral and peri-coital vaginal administration for prevention of pregnancy. J Obstet Gynaecol 2011; 31(8): 703–707.
- Gatzke N, Johnson L. Ectopic pregnancy: a red flag diagnosis. Nurse Pract 2014; 39(12): 42–47.
- 12. Farquhar CM. Ectopic pregnancy. Lancet 2005; 366(9485): 583-591.
- Zhang J, Li C, Zhao WH, et al. Association between levonorgestrel emergency contraception and the risk of ectopic pregnancy: a multicenter case—control study. Sci Rep 2015; 5: 8487.
- Westley E, Glasier A. Emergency contraception: dispelling the myths and misperceptions. Bull World Health Organ 2010; 88(4): 243–244.
- Kisa S, Zeyneloğlu S, Yilmaz D, Verim E. Examining barriers to emergency contraception use. Appl Nurs Res 2012; 25(3): 158–163.
- American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 94: medical management of ectopic pregnancy. *Obstet Gynecol* 2008; 111: 1479–1485.
- Li C, Zhao WH, Meng CX, et al. Contraceptive use and the risk of ectopic pregnancy: a multi-center case-control study. PLoS One 2014; 9(12: e115031).
- Meng CX, Gemzell-Danielsson K, Stephansson O, Kang JZ, Chen QF, Cheng LN. Emergency contraceptive use among 5677 women seeking abortion in Shanghai, China. Hum Reprod 2009; 24(7): 1612–1618.
- 19. Wang D. Contraceptive failure in China. Contraception 2002; 66(3): 173-178.
- Swahn ML, Westlund P, Johannisson E, Bygdeman M. Effect of postcoital contraceptive methods on the endometrium and the menstrual cycle. *Acta Obstet Gynecol Scand* 1996; 75: 738–744.
- Gemzell-Danielsson K, Rabe T, Cheng L. Emergency contraception. Gynecol Endocrinol 2013; 29: 1–14.
- Wanggren K, Stavreus-Evers A, Olsson C, Andersson E, Gemzell-Danielsson K. Regulation of muscular contractions in the human Fallopian tube through prostaglandins and progestagens. *Hum Reprod* 2008; 23: 2359–2368.
- Mahmood T, Saridogan E, Smutna S, Habib AM, Djahanbakhch O. The effect of ovarian steroids on epithelial ciliary beat frequency in the human Fallopian tube. *Hum Reprod* 1998; 13: 2991–2994.
- Shaw JL, Dey SK, Critchley HO, Horne AW. Current knowledge of the aetiology of human tubal ectopic pregnancy. *Hum Reprod Update* 2010; 16: 432–444.
- Gemzell-Danielsson K, Meng CX. Emergency contraception: potential role of ulipristal acetate. Int J Womens Health 2010; 2: 53–61.
- Cheng L, Che Y, Gülmezoglu AM. Interventions for emergency contraception. Cochrane Database Syst Rev 2012; 8: CD001324.
- Wood AJ, Drazen JM, Greene MF. The politics of emergency contraception. N Engl J Med 2012; 366(2): 101–102.
- Wan RS, Lo SS. Are women ready for more liberal delivery of emergency contraceptive pills? *Contraception* 2005; 71(6): 432–437.
- Chen Y, Cheng L, Kang J. Evaluation of emergency contraception pills among women with induced abortion in Shanghai. *Chin J Fam Plann* 2006; 2(14): 93–95.
- Nelson AL, Jaime CM. Accuracy of information given by Los Angeles County pharmacies about emergency contraceptives to sham patient in need. Contraception 2009; 79: 206–210.
- Committee on Health Care for Underserved Women. ACOG Committee Opinion Number 542: access to emergency contraception. Obstet Gynecol 2012; 120(5): 1250–1253.
- Xu J, Cheng L. Awareness and usage of emergency contraception among teenagers seeking abortion: a Shanghai survey. Eur J Obstet Gynecol Reprod Biol 2008: 141(2): 143–146.
- Lo SS, Kok WM, Fan SY. Emergency contraception: knowledge, attitude and prescription practice among doctors in different specialtiesin Hong Kong. J Obstet Gynaecol Res 2009; 35(4): 767–774.