

# Pregnancy rate after emergency contraception with single-dose oral levonorgestrel in Japanese women

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## Abstract

**Aim:** To evaluate the pregnancy rate in Japanese women treated with levonorgestrel for emergency contraception.

**Methods:** This retrospective record-based medical study included 1000 women who visited our clinic for emergency contraceptive treatment with 1.5 mg single-dose oral levonorgestrel, followed by 50 µg hormonal oral contraceptive from May 2011 to December 2017. The outcomes of the emergency contraceptive treatment were recorded at a follow-up visit, and descriptive statistics were obtained.

**Results:** The number of women treated with levonorgestrel at the clinic increased from 2011 to 2015, but there was no subsequent increase thereafter. Most women were in their 20s (57.4%), followed by their 30s (19.3%) and teens (18.3%). Of the 1000 women treated with levonorgestrel, 659 were followed up. Among the 659 women with follow-up data, 16 were pregnant (2.4%), of whom 11 underwent abortions, three had miscarriages, and two delivered at term. The timing of unprotected sexual intercourse relative to the estimated ovulation date among the pregnant women ranged from –3 to 23 days. The most commonly used contraceptive method before the emergency contraceptive visit was condoms (89.3%, 887/993). No new safety concerns were identified throughout the study period.

**Conclusion:** The pregnancy rate after levonorgestrel treatment in Japanese women was low, and similar to that reported in previous studies. Information on contraceptive methods and emergency contraception with levonorgestrel needs to be better disseminated among women of childbearing age.

**Key words:** emergency contraceptive, hormonal oral contraceptive, levonorgestrel, pregnancy rate, sex education.

## Introduction

Emergency oral hormonal contraceptive methods have evolved since the first use of high-dose estrogen in the 1960s,<sup>1</sup> followed by the Yuzpe regimen (medium pill, 100 µg ethinylestradiol combined with 1.0 mg of dl-norgestrel, twice 12 h apart) in the 1970s<sup>2</sup> and levonorgestrel in the 1990s.<sup>3,4</sup> In a large-scale study, the World Health Organization reported that the levonorgestrel regimen (0.75 mg, repeated 12 h later) was better tolerated, more effective, and caused fewer side effects, such as nausea and vomiting than the Yuzpe regimen

(ethinylestradiol 100 µg plus levonorgestrel 0.5 mg, repeated 12 h later).<sup>3</sup> Levonorgestrel (two 0.75 mg doses 12 h apart) prescription was approved as an emergency contraceptive method in the United States in 1999 and has been marketed in many countries,<sup>5–9</sup> and the same regimen was subsequently approved as an over-the-counter drug in 2006. It was shown in 2002 that a single 1.5 mg oral levonorgestrel dose within 72 h of sexual intercourse could substitute for two 0.75 mg doses 12 h apart,<sup>4</sup> and this new regimen was approved as an over-the-counter treatment in the United States in 2013.

Received: March 17 2019.

Accepted: June 12 2019.

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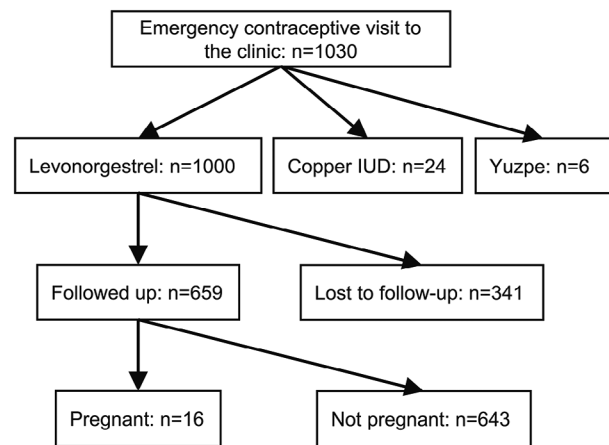
In Japan, two 0.75 mg doses of levonorgestrel 12 h apart was first approved in 2011, followed by approval of the 1.5 mg regimen in 2016. The 'Guidelines on proper use of emergency contraceptive method' issued by the Japan Society of Obstetrics and Gynecology recommended single-dose levonorgestrel as the standard for emergency contraception in May 2011.<sup>10</sup> Notably, however, the approval of levonorgestrel as an over-the-counter drug is still pending in Japan.

Because levonorgestrel was approved relatively late in Japan compared with other countries, the medication's efficacy and safety in a real clinical setting among Japanese women has only been addressed in a review.<sup>11</sup> We have been treating women who visited our clinic for emergency contraceptive treatment, most of whom received 1.5 mg levonorgestrel. We considered that the subsequent pregnancy rate calculated on the basis of these data would provide valuable information on the real-world efficacy and tolerance of levonorgestrel. The results of this study also emphasize the need to improve the awareness of and access to levonorgestrel as an effective and safe emergency contraceptive method, among physicians, teachers, and women of childbearing age.

## Methods

This retrospective record-based medical study aimed to evaluate the pregnancy rate in Japanese women after emergency contraceptive treatment with levonorgestrel. A total of 1030 women visited our clinic for emergency contraceptive treatment from May 30, 2011 to December 25, 2017. The following information was recorded for each patient at their first visit: standard demographic information, smoking status, marital status, partner's age, age at first sexual intercourse, pregnancy/delivery history, reason for requesting emergency contraceptive, source of information about the emergency contraceptive and time from estimated ovulation to unprotected sexual intercourse (UPSI) and from emergency contraceptive treatment to UPSI.

Patients were treated with one of the following contraceptive methods: single treatment with oral 1.5 mg levonorgestrel, Yuzpe regimen or copper intrauterine device (IUD), plus 50 µg hormonal oral contraceptive (OC) starting on the day after the emergency contraceptive treatment, in accordance with the standard treatment protocol issued by Japan Society of Obstetrics and Gynecology and Japan Association of Obstetricians and Gynecologists.<sup>12</sup> Patients were instructed to visit the clinic for a follow-up after 3–4 weeks. Additional



**Figure 1** Participants' disposition. IUD, intrauterine device.

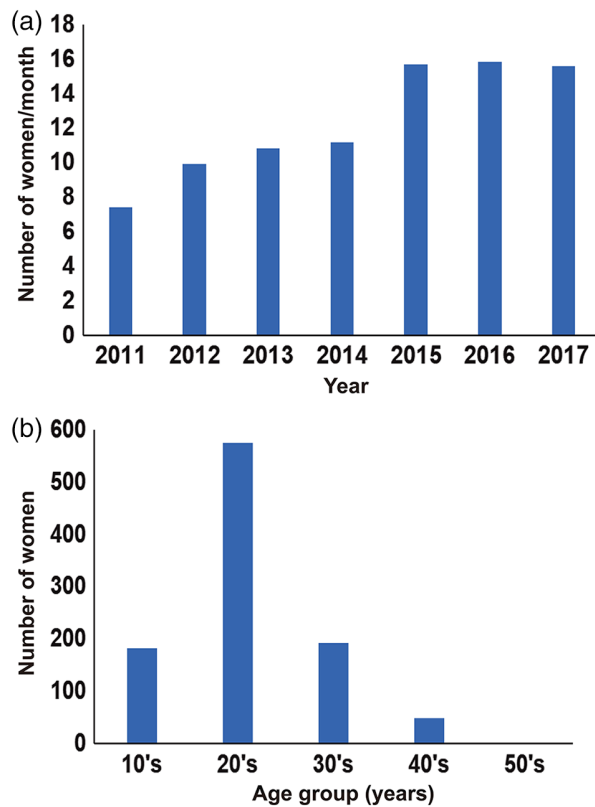
information (contraceptive methods after the emergency contraceptive treatment, side effects, and pregnancy outcome) were recorded at the follow-up visit.

Each patient was given an identification number, and demographic and outcome information were analyzed as of February 2, 2018. The numbers of women who received levonorgestrel were obtained according to the year of visit and patient's age group. Descriptive statistics were obtained for pregnant, non-pregnant, and all women. No statistical between-group analysis was carried out because of the small sample size of the pregnant group.

## Results

Among 1030 women who visited the clinic from May 2011 to December 2017, 1000 were treated with a single oral 1.5 mg levonorgestrel tablet, 24 with a copper IUD and six with the Yuzpe regimen (Fig. 1). Of the 1000 women who received levonorgestrel, 977 were treated with levonorgestrel within 72 h of UPSI, 20 within 4–6 days, and the interval was unknown in the other three women.

The number of women treated with levonorgestrel at the clinic increased each year up to 2015, but remained similar thereafter (Fig. 2a). Most women were in their 20s (57.4%, 574/1000 women), followed by their 30s (19.3%, 193/1000) and teens (18.3%, 183/1000) (Fig. 2b). The mean patient age was  $25.5 \pm 6.8$  years (Table 1). Commonly used contraceptive methods before the visit to the clinic were condoms (89.3%, 887/993), withdrawal (4.5%, 45/993), and OC (4.2%, 42/993), but no women used an IUD or other intrauterine system (Table 2).



**Figure 2** Numbers of women treated with levonorgestrel according to year (a) and age group (b).

The most commonly used contraceptive method leading to the visit to the clinic for emergency contraceptive treatment was condoms (68.7%, 684/995), followed by no contraceptive (21.5%, 214/995) and withdrawal (8.1%, 81/995) and the most common reason for the clinic visit was condom-related incidences

(condom breakage, 33.3%, 330/992; condom slipped off, 28.4%, 282/992). Of the 1000 women, 47.8% (474/991) obtained their information on emergency contraceptives through the internet, 23.3% (231/991) from friends, 9.4% (93/991) from partners, and 8.7% (86/991) from physicians (Table 2).

As of February 28, 2018, 341 women were lost to follow-up with unknown pregnancy outcome and 659 women visited the clinic for a follow-up (65.9%). Among these 659 women, 16 pregnancies were observed (2.4%, 16/659), of whom 11 underwent abortions, three had miscarriages, and two delivered. Fifteen pregnant women were treated with levonorgestrel within 55 h of UPSI. All except one pregnant patient started OC the day after levonorgestrel administration. The time from UPSI to ovulation was between -3 and 23 days in the 16 pregnant women, but no patient had UPSI more than 4 days before her estimated ovulation. Of the two delivered women, one was married and another was single at a time of emergency contraceptive visit, but both were married when they delivered (Table 3). There were no notable differences in characteristics, such as age and smoking status, between pregnant and non-pregnant women (Table 1).

## Discussion

Our clinic has been providing emergency contraception with 1.5 mg levonorgestrel since May 2011, when levonorgestrel was approved and became available from ASKA Pharmaceutical Co., Ltd. We analyzed the efficacy of levonorgestrel for preventing pregnancy when 1000 women had been treated, to provide a large

**Table 1** Characteristics of participants treated with levonorgestrel according to pregnancy status

Characteristic	Followed-up ( <i>n</i> = 659)		Total ( <i>n</i> = 1000)
	Pregnant ( <i>n</i> = 16)	Not pregnant ( <i>n</i> = 643)	
Age at first clinic visit (years), <i>n</i>	16	643	1000
	27.1 ± 6.6	25.6 ± 6.9	25.5 ± 6.8
Age at first sexual intercourse (years), <i>n</i>	16	637	987
	18.0 ± 1.7	18.0 ± 2.8	17.8 ± 2.7
Paternal age (years), <i>n</i>	16	584	883
	31.2 ± 7.3	27.8 ± 8.1	28.0 ± 8.0
Number with prior delivery, <i>n</i>	16	643	998
	0.9 ± 1.2	0.4 ± 0.8	0.4 ± 0.9
Number with prior D&C, <i>n</i>	16	643	998
	0.4 ± 0.8	0.3 ± 0.6	0.3 ± 0.7
Smoking status, <i>n</i>	16	642	998
Yes, <i>n</i> (%)	3 (18.8)	142 (22.1)	246 (24.6)
No <i>n</i> (%)	13 (81.3)	500 (77.9)	752 (75.3)

D&C, dilation and curettage. Values presented as mean ± standard deviation unless otherwise specified.

**Table 2** Characteristics of participants treated with levonorgestrel

Characteristic	Total ( <i>n</i> = 1000)
Usual contraceptive method, <i>n</i> (%)	993
Condom	887 (89.3)
Withdrawal	45 (4.5)
Hormonal oral contraceptives	42 (4.2)
None	17 (1.7)
Other	2 (0.2)
Contraceptive method leading to the clinic visit, <i>n</i> (%)	995
Condom	684 (68.7)
None	214 (21.5)
Withdrawal	81 (8.1)
Other	8 (0.8)
Intrauterine system	5 (0.5)
Reason for clinic visit, <i>n</i> (%)	992
Condom breakage	330 (33.3)
Condom slipped off	282 (28.4)
No contraceptive used	186 (18.8)
Withdrawal	67 (6.8)
Other	127 (12.8)
Source of information on emergency contraceptives, <i>n</i> (%)	991
Internet	474 (47.8)
Friends	231 (23.3)
Partner	93 (9.4)
Physician	86 (8.7)
School education	58 (5.9)
Hospital staff	26 (2.6)
Family members	12 (1.2)
Books	9 (0.9)
TV	2 (0.2)

enough sample size to produce meaningful results in a real clinical setting. In addition, we considered that the issue was clinically significant given that some women became pregnant and delivered despite treatment with levonorgestrel within 72 h.

The pregnancy rate in this study was 2.4%, which was consistent with previous reports (0.7–2.6%).<sup>4,13–15</sup> Similar pregnancy rates were reported in Japanese women in post-marketing surveillance (0.7%, 4/570 women, unpublished report; ASKA Pharmaceutical Co. Ltd.) and in a phase III study (1.6%, 1/63 women, unpublished report; Sosei Co. Ltd.) with smaller sample sizes. The present and previous results thus suggest that emergency contraception with levonorgestrel is a highly effective method for preventing pregnancy.

The timing of UPSI relative to the expected ovulation date may affect the success/failure of emergency contraceptive treatment with levonorgestrel. Sexual intercourse within 6 days before ovulation was previously shown to result in a high pregnancy rate.<sup>16</sup> Indeed, nine of the 16 pregnant women in the current study had

UPSI within 6 days before their expected ovulation day. Because levonorgestrel delays or inhibits ovulation by suppressing luteinizing hormone,<sup>17</sup> the relative timing of UPSI, activation of luteinizing hormone, and treatment with levonorgestrel could have affected the pregnancy outcome. However, similar data were not collected for non-pregnant women in this study, and more data are therefore needed to support this interpretation. Notably, insertion of a copper IUD might have prevented pregnancy in a few women with a past delivery experience who were treated with levonorgestrel more than 10 days after UPSI, given that copper IUDs have been shown to prevent pregnancy even when inserted more than 10 days after UPSI.<sup>18,19</sup>

Two of the 16 pregnant women in the current study gave birth; no clinically significant issues with the delivery process or the newborns were reported, suggesting that levonorgestrel failure had no clinical adverse effects on the newborns.

The Public Health Administration statistics provided by the Ministry of Health, Labour and Welfare in Japan have shown that the number of abortions has been declining in recent years (e.g., 226 878 women in 2009 vs 186 253 in 2013), although the number of abortions carried out each year remains high.<sup>20</sup> Approximately 880 women visited our clinic for an abortion during the study period, confirming the high number of abortions. Although the reasons for the abortion visits were not analyzed in this study, lack of knowledge and access to emergency contraceptive methods should be taken into consideration. Promoting sex education to improve awareness of emergency contraception could have prevented women from seeking surgical termination, as well as financial distress over the associated medical costs. Notably, medical expenses associated with abortion, except in rape cases, are not covered by health insurance in Japan.<sup>12</sup>

According to the latest survey carried out every 2 years by the Japan Family Planning Association, only 50% of women and 40% of men in 2017 were aware of the available emergency contraceptive methods.<sup>21</sup> In Japan, no specific actions leading to pregnancy, or information on contraceptive and emergency contraceptive methods, are included in the compulsory sex education curriculum.<sup>22,23</sup> Indeed, the present results showed that over 70% of women learned about emergency contraceptive methods via the internet or friends, compared with less than 6% at school. The scant school education on pregnancy and contraception suggests that broader platforms are urgently needed to inform people, women in particular, about all available contraceptive options.

Table 3 Characteristics of participants who were pregnant after emergency contraception with levonorgestrel

Subject ID	Age (years)	Prior pregnancy	Prior delivery	Contraceptive <sup>†</sup>	Source of information	Between estimated ovulation and UPSI (days)	Initiation of emergency contraceptive treatment after UPSI (hours)	Contraceptive after the emergency clinic visit	Outcome	Marital status
1	28	1	0	Condom	Partner	-3	34	OC	Miscarriage, 5 w	Single
2	22	0	0	Condom	Partner	-2	13	OC	Miscarriage, 7 w	Single
3	37	1	1	None	Internet	-2	34	OC	D&C, 6 w	Married
4	40	2	2	Condom	Internet	-1	8	OC	D&C, 7 w	Married
5	25	3	2	None	Friends	-1	13	-	D&C, 6 w	Divorced
6	35	3	3	Condom	Internet	0	31	OC	D&C, 6 w	Married
7	33	3	3	Condom	Internet	0	33	OC	D&C, 6 w	Married
8	20	0	0	None	Partner	0	55	OC	D&C, 7 w	Single
9	30	0	0	Withdrawal	Internet	0	93	OC	D&C, 7 w	Single
10	24	1	1	Withdrawal	Internet	2	12	OC	Delivered	Married
11	20	0	0	Condom	Friends	3	6	OC	D&C, 7 w	Single
12	19	1	0	Condom	Partner	3	18	OC	D&C, 8 w	Single
13	19	0	0	Condom	School education	4	7	OC	D&C, 6 w	Single
14	30	4	3	Condom	Internet	17	52	OC	D&C, 7 w at another clinic	Married
15	24	3	0	Condom	Physician	18	14	OC	Miscarriage, 6 w	Single
16	28	0	0	Condom	Internet	23	11	OC	Delivered	Married before delivery

D&C, dilation and curettage; OC, oral contraceptive; UPSI, unprotected sexual intercourse; w, week.; †Contraceptive that led to the clinic visit for the emergency contraceptive treatment.; Day 0 = estimated ovulation day. -: data not available.

The most commonly used contraceptive method in the current study was condoms (89.3%), with only 4.2% of women using OCs, supporting the fact that Japanese people tend to rely on condoms to avoid unwanted pregnancies. However, as also indicated in this study, over 60% of women who visited the clinic for emergency contraceptive treatment did so as a result of condom-related incidences, indicating that condoms do not provide a reliable contraceptive method. Better education programs on contraceptive methods, such as OC and emergency contraception, need to be available to the general public, especially women, to allow them to become more proactive and responsible in implementing contraceptive methods.

Of 661 women with available records, no side effects were reported in 638 (96.5%) women and no new safety concerns were identified,<sup>4</sup> indicating that emergency contraceptive treatment with a single 1.5 mg dose of levonorgestrel was safe and well tolerated in Japanese women.

This study was limited by the fact that a proportion of the pregnancies prevented was not assessed. Furthermore, this was a single-center study, which might have caused bias; however, the sample size was large enough to assess the outcome in current clinical practice. Another limitation is that the efficacy of levonorgestrel was assessed only by the pregnancy rate in this study. Since the clinical efficacy of emergency contraceptive methods in general is often overestimated, patients should be notified that the actual clinical efficacy may be lower than expected, and what options, such as copper IUD, are available.

In conclusion, the results of this study showed that the pregnancy rate after levonorgestrel treatment in Japanese women in a real clinical setting was low and similar to that reported in previous studies. Information on regular contraceptive methods and emergency contraception with levonorgestrel needs to be better disseminated among women of childbearing age.

## Acknowledgments

The author thanks ASCA Corporation for providing medical writing and editorial support, funded by ASKA Pharmaceutical Co., Ltd.

## Disclosure

None declared.

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