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SYSTEMATIC REVIEW

A Systematic Review and Meta-analysis of the Adverse Effects of Levonorgestrel Emergency Oral Contraceptive

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Abstract

Introduction The levonorgestrel oral emergency contraceptive is well tolerated and effective, however its use is still limited, mainly due to safety concerns.

Objective This systematic review and meta-analysis aimed to summarize current evidence regarding the adverse events, and their prevalence, reported during the use of oral levonorgestrel emergency contraceptives.

Methods Four electronic databases and the US FDA Adverse Event Reporting System (FAERS) Public Dashboard were searched. Studies that reported or investigated safety outcomes or adverse reactions during the use of levonorgestrel as an emergency oral contraceptive were included. Data on study design, demographics of levonorgestrel and the control cohort, and reported adverse effects were extracted.

Results A total of 47 articles were included in this systematic review, from which it was shown that most of the adverse reactions were common and not serious. Uncommon adverse reactions identified included anorexia, ectopic pregnancy, exanthema, chloasma, miscarriage, and weight gain. Multiple serious adverse events, including convulsion, ectopic pregnancy, febrile neutropenia, stroke, abdominal hernia, anaphylaxis, cancer, ovarian cyst rupture, serious infections, and suicidal ideation, were reported. In addition, the prevalence of adverse events after a levonorgestrel 0.75 mg two-dose regimen and a levonorgestrel 1.5 mg single-dose regimen were not statistically different ($p > 0.05$).

Conclusions The most common adverse effects of levonorgestrel were not serious. This systematic review shows that data regarding the adverse reactions of repeated use of levonorgestrel are scarce. Studies on the multiple uses of levonorgestrel emergency contraception are still required to ensure its safety.

1 Introduction

Levonorgestrel has been extensively used as emergency contraception and is available as intrauterine devices (IUDs) and oral contraceptives [1]. Oral levonorgestrel is most commonly administered as a 0.75 mg tablet within 72 h postcoital, while the second tablet, which also contains 0.75 mg of levonorgestrel, is administered 12 h after the first dose [2]. Other variations in the dosing regimen include taking the first tablet within 120 h postcoital, taking the second tablet 24 h after the first tablet, or taking two 0.75 mg tablets within 72 h postcoital [2]. Despite the fact that the levonorgestrel oral emergency contraceptive is well tolerated and effective as postcoital oral contraception [3], its use as an emergency contraceptive is still limited. One reason for this is that the efficacy of the levonorgestrel emergency oral contraceptive is less than the combined oral contraceptive. While the failure rate of the combined oral contraceptive ranges from 0.75 to 1.67% [4], the failure rate of the levonorgestrel emergency oral contraceptive ranges from 0.6 to 3.1%, which is higher than ulipristal acetate (failure rate 0.9–1.2%) and the copper IUD (failure rate: < 0.1%) [5]. In addition, there is evidence that

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Key Points

Most levonorgestrel emergency oral contraceptive adverse reactions were common and not serious.

The prevalence of adverse events of a levonorgestrel 0.75 mg two-dose regimen and a levonorgestrel 1.5 mg single-dose regimen was not statistically different.

The use of levonorgestrel emergency oral contraceptives should be promoted in populations that are in need but who also have safety concerns.

repeated unprotected intercourse in the same menstrual cycle was associated with emergency contraceptive failure [6].

While efficacy is a concern for limiting use of the levonorgestrel oral contraceptive, safety is more concerning. Patients [7–9] and pharmacists [10] may feel that levonorgestrel oral emergency contraceptives are not well tolerated. In some women, minor common adverse effects such as nausea or headache can prevent them from using the product [11]. Moreover, special concerns that levonorgestrel oral emergency contraceptives can cause serious adverse effects, including abortion, infertility, blood clots, and even cancer, are common among women [7, 12]. Scientific evidence also shows conflicting evidence regarding the safety of oral levonorgestrel. For example, several observational studies showed that the use of oral levonorgestrel may cause ectopic pregnancy [13–15], but multiple systematic reviews suggested otherwise [3, 16, 17]. Another example is venous thromboembolism. Several studies suggested that levonorgestrel was associated with venous thromboembolism [18–21]; however, a review demonstrated that the effect of progestin on venous thromboembolism was inconclusive and the association between venous thromboembolism and levonorgestrel found in several observational studies might have been influenced by the effect of confounders, e.g. new use, older age, obesity, family history of venous thromboembolism, or prolonged immobilization [22]. In addition, several studies suggested that knowledge of oral emergency contraceptives was inadequate among healthcare professionals [23–26] and policymakers [27]. Therefore, this systematic review and meta-analysis aimed to summarize current evidence regarding adverse events and their prevalence reported during the use of oral levonorgestrel emergency contraceptives.

2 Methods

2.1 Data Sources and Search strategy

A systematic literature search was performed of the MEDLINE, Scopus, Science Direct, and CINAHL Complete databases from conception to October 2019, using the terms (‘postcoital oral contraceptive” [e.g. morning-after pills] OR ‘levonorgestrel’) AND (‘case report’ OR ‘adverse reaction’ [e.g. adverse drug reaction]) without applying language restrictions. Synonyms of search terms suggested by the search engines were used. The full search strategies are provided in Electronic Supplementary Material 1. References for related review articles, letters, and protocols were searched for potential pertinent studies.

Data from a spontaneous reporting system, the US FDA Adverse Event Reporting System (FAERS) Public Dashboard, were also retrieved to further capture the adverse events of levonorgestrel. The search term ‘levonorgestrel’ was used and an additional filter, ‘reason for use’ as oral contraception, was applied. The adverse event data of levonorgestrel in the FAERS Public Dashboard, available from 1971 to 2019, were retrieved. It should be noted the FDA does not require that a causal relationship between a drug and event be proven. Moreover, incidence, risk assessment, and risk ranking cannot be provided based on FAERS data.

2.1.1 Inclusion and Exclusion Criteria

Studies were included in this meta-analysis if they were (1) human studies; (2) studies that explicitly indicate levonorgestrel as the exposure; and (3) studies that explicitly indicate safety outcomes or adverse reactions during the use of levonorgestrel. Studies were excluded if they were (1) not research articles; (2) studies whose participants used non-oral drug delivery systems for levonorgestrel; (3) studies that used levonorgestrel for purposes that were not emergency contraception (e.g. as progestin-only pills); (4) studies that used levonorgestrel as a combined oral contraceptive; or (5) conducted in males. In the case of case reports, case series, and studies that reported data that could not be used to calculate pooled data, these were included for the systematic review but not the meta-analysis. Figure 1 shows the preferred reporting items for systematic reviews and meta-analysis (PRISMA) diagram of the systematic literature review process.

2.2 Data Extraction

Articles retrieved from searching were stored in a citation manager (EndNote X7, Thomson Reuters, New York, NY, USA). After the removal of redundant articles, titles and

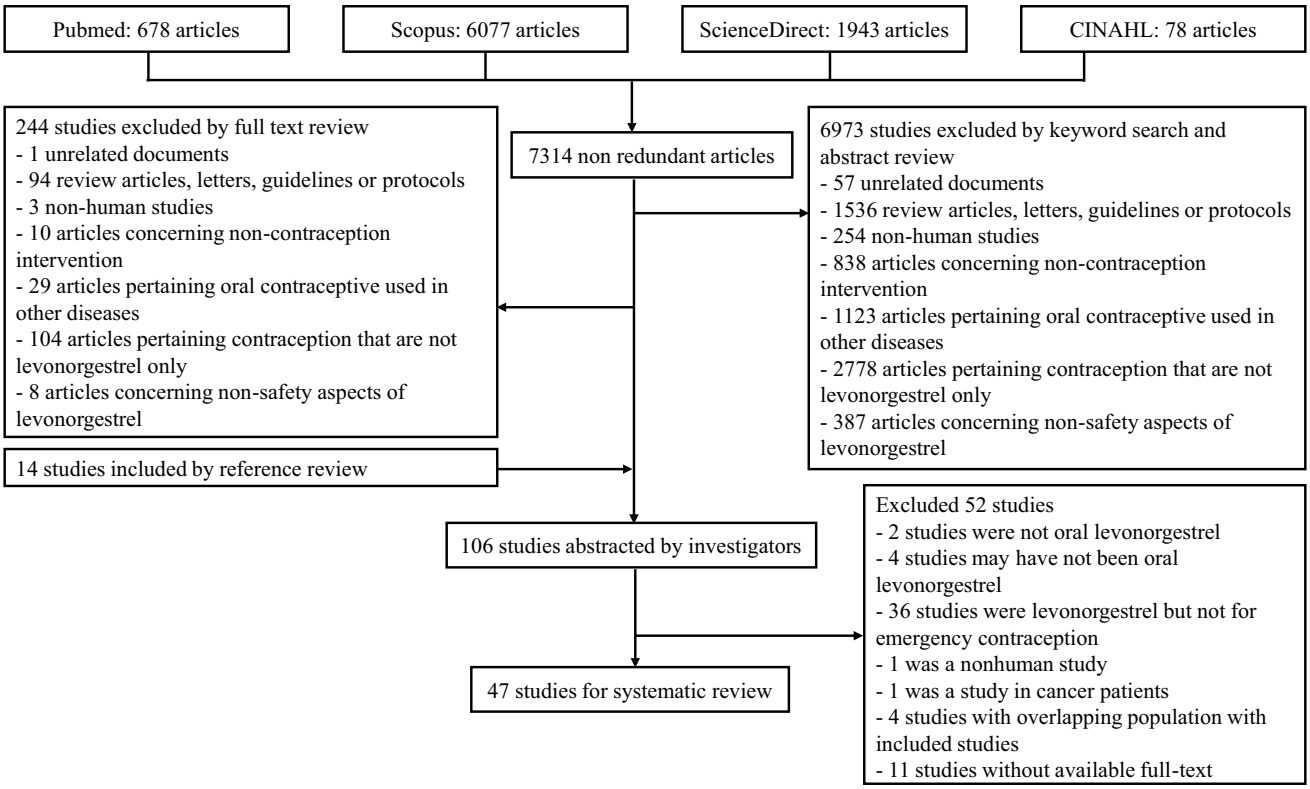

Fig. 1 PRISMA diagram for systemic review of the adverse effects of levonorgestrel emergency oral contraceptive

abstracts of the remaining articles were reviewed by the first author by searching for specific words for the exclusion (e.g. to exclude intrauterine levonorgestrel, words such as intrauterine, devices, and IUD were searched). The remaining abstracts were reviewed. For non-English-language articles, English abstracts and Result sections in full texts were used to determine if further translation was necessary. For the abstraction process, the abstraction form was designed by the first author and reviewed by the coauthor. Data on study design, location, patient demographics, dosage regimens of levonorgestrel, timing after coitus, types of adverse reactions and their corresponding prevalence, and potential biases and confounders in every study were independently extracted by the first and second authors. Any disagreement was resolved by consensus. For the reporting system, the severity and duration of the adverse reactions were reported according to the definition of the frequency of adverse drug reactions developed by the Council for International Organizations of Medical Sciences [28]. Serious adverse reactions were "any untoward medical occurrence that at any dose results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability or incapacity". Very common, common (or frequent), uncommon (or infrequent), rare, and very rare adverse reactions occur at a frequency higher than 1/10; less than 1/10 to higher than 1/100; less than 1/100 to higher than 1/1000; less than 1/1000 to higher than 1/10,000; and less than 1/10,000, respectively.

2.3 Risk of Bias

The risk of bias was determined using different tools according to the type of included studies. Clinical trials, observational studies, and cross-sectional studies were evaluated using the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials (CCRAB-RCT) [29], Newcastle–Ottawa Quality Assessment Scale (NOS) [30], and a modified Newcastle–Ottawa Quality Assessment Scale for cross-sectional studies [31], respectively. These tools were well-validated and recommended for use in systematic reviews and meta-analyses [32]. Case reports and case series were assessed using a tool modified from Pierson's guide for evaluating the validity and educational value of a case report [33], Bradford Hills criteria [34], and Newcastle–Ottawa scale [30], which was proposed by Murad et al. [35]. Thresholds for converting CCARB-RCT and NOS results to the Agency for Healthcare Research and Quality (AHRQ) standard of 'good', 'fair', and 'poor' quality designations have been described by Likis et al. [36]. For the tool proposed by Murad et al., the questions with positive answers (e.g. yes or clear evidence, or no alternative explanation) were converted to 1. The total scores of 1–3, 4–5,

and 6–8 were then converted to 'good', 'fair', and 'poor', respectively.

2.4 Statistical Methods

Only studies reporting the prevalence of adverse reactions were included in this meta-analysis. The binary random-effects model using the DerSimonian–Laird method was created using OpenMetaAnalyst for Windows 8 [37]. The I^2 statistic was used to assess the heterogeneity of the underlying population. An I^2 of < 25% was negligible heterogeneity, whereas I^2 values > 75% were highly heterogeneous [38]. Stratification by levonorgestrel dose was planned prior to the analysis. The statistical significance of the data was considered at an α level of 0.05. Since the 95% confidence intervals (CIs) were aligned to detect the statistical difference in each data point, the exact *p*-values could not be reported.

3 Results

3.1 Study Characteristics

The systematic literature search retrieved 7314 non-redundant articles. According to the inclusion and exclusion criteria, 47 articles were included for the systematic review. There were 15 case reports or case series, 15 observational studies, and 17 clinical studies (Table 1). The quality of the included articles varied (a summary of the study quality is reported in Table 1). Of the 47 articles, 30, excluding case reports, were included in the meta-analysis (Table 2). Twenty-three studies had < 1000 participants (median 330 participants [range 25–4631]). The 30 articles were conducted in America (Brazil, USA, Peru), Europe (Italy, Norway, Poland, Spain, Sweden, UK), Asia (China, India, Iran, Japan, Thailand), Africa (Nigeria, Uganda), and Australia. The mean age median in the included studies was 27 years (range 13–48 years). Seventeen studies were conducted using a two-dose regimen of levonorgestrel 0.75 mg tablets [39–55], with a median time between doses of 12 h (range 8–12 h). Eleven studies were conducted using a single-dose regimen of two tablets of levonorgestrel 0.75 mg [44, 53, 56–64]. Four studies did not report the dosing regimen used in their studies [65–68]. For the studies that reported the dosing regimen, participants used levonorgestrel within 3–72 h after unprotected sex (range 72 h). The median exposure frequency to levonorgestrel throughout the study was a single dose (range 1–13 times). The median study duration was 6 weeks (range 0.4–65.2 weeks). We inferred that the studies included in this meta-analysis represented a global population that used the clinically relevant levonorgestrel dosing regimen for emergency contraception. The duration of the included studies was sufficient to capture short-term uncommon adverse reactions. In addition, it was also possible that this meta-analysis might have captured very rare adverse reactions since the total number of patients in this meta-analysis was higher than 20,000.

3.2 Safety of Levonorgestrel Emergency Oral Contraceptives in Users

From the systematic review, adverse reactions that were found could be classified into gynecological adverse reactions, neurological adverse reactions, gastrointestinal adverse reactions, pregnancy and neonatal complications, and miscellaneous adverse reactions. Most adverse reactions were common and not serious. Uncommon adverse reactions identified included anorexia [58], ectopic pregnancy [68], exanthema [58], chloasma [64], miscarriage [68], and weight gain [64], while serious adverse reactions identified included convulsion, ectopic pregnancy, febrile neutropenia, and stroke [68]. In addition, three case reports regarding the adverse reaction of levonorgestrel were identified during the systematic search. The first reported a 23-year-old woman experiencing a stroke within 24 h after using levonorgestrel 1.5 mg [69]. Second, a case of venous thrombosis confirmed by a venous Doppler ultrasound and magnetic resonance venography was reported in a 22-year-old woman who used levonorgestrel 72 h prior to the occurrence of venous thrombosis [70]. The other case series presented a case of a patient in her 20 s who took a single tablet of levonorgestrel emergency contraception and had autoimmune progesterone dermatitis confirmed by skin prick and intradermal skin testing to progesterone [71].

Adverse reactions included in the meta-analysis were very common and common adverse reactions. Very common adverse reactions during the use of levonorgestrel emergency contraception were gynecological adverse reactions, including alteration of menstrual flow (46.8%; 95% CI 38.5–55.1%; $n = 1$), bleeding (31.0%; 95% CI 29.3–32.7%; $n = 2$, $I^2 = 0.0\%$), hypomenorrhea (26.2%; 95% CI 21.9–30.6%; $n = 2$, $I^2 = 0.0\%$), intermenstruation spotting (23.5%; 95% CI 7.8–39.2%; $n = 5$, $I^2 = 98.5\%$), and early menstruation (18.5%; 95% CI 5.1–32.0%; $n = 2$, $I^2 = 88.0\%$). The detailed summary of the pooled frequency of adverse reactions is shown in Table 2. In brief, the most commonly reported gynecological safety outcomes with a sufficient number of publications for the stratification analysis were breast pain (8.3%; 95% CI 5.8–10.7%; $n = 16$, $I^2 = 98.0\%$) and late menstruation (6.5%; 95% CI 4.7–8.4%; $n = 7$, $I^2 = 85.4\%$). Neurological outcomes included headache (12.4%; 95% CI 9.8–14.9%; $n = 24$, $I^2 = 98.6\%$) and dizziness (10.8%; 95% CI 8.7–12.9%; $n = 21\%$, $I^2 = 96.3\%$). Gastrointestinal outcomes included nausea (15.0%; 95% CI 11.9–18.1%;

Table 1 Description of included studies

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Rodríguez de Antonio et al. 2011 [69]	Case report (fair)	Spain (2011)	Dose = 1.5 mg, single dose Time limit after coitus = ND *n* = 1 Age (years) = 23 Exposure frequency = single dose Follow-up duration (hours) = ND	NA	Stroke
Arowojolu and Okewole [56]	Prospective observational study (good)	Nigeria (2004)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 72 *n* = 544 Age (years) = 26.6 ± 7.2 Exposure frequency = single dose Follow-up duration (weeks) = 6	NA	*Primary objective:* Vaginal bleeding *Secondary objective:* Nausea, vomiting, dizziness, headache, breast tenderness, lower abdominal pains
Basu and Candelier, 2005 [72]	Case report (poor)	UK (2005)	Dose = 0.75 mg, two doses Time between doses (hours) = ND Time limit after coitus (hours) = 72 *n* = 1 Age (years) = 27 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Bhattacharjee et al. 1987 [39]	Prospective observational study (fair)	Multicenter: WHO (1987)	Dose = 0.75 mg, two doses Time between doses (hours) = 24 Time limit after coitus (hours) = 8 *n* = 259 Age (years) = 25.7 ± 4.7 Exposure frequency (times) = 7.5 ± 2.6 Follow-up duration (menstrual cycles) = 6–7	NA	Nausea, headache, dizziness, lower abdominal pain, backache, breast tenderness/engorgement, vomiting

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Byamugisha et al. 2010 [57]	Randomized controlled trial (fair)	Uganda (2005–2006)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 72 *n* = 167 Age (years) = 21.1 ± 3.52 Exposure frequency = ND Follow-up duration (months) = 12	Ethinylestradiol 0.03 mg and norgestrel 0.3 mg/tablet, two doses *n* = 177 Age (years) = 22.2 ± 3.46 (mean ± SD) Exposure frequency = ND Duration (months) = 12	*Not significantly different:* Nausea, vomiting, dizziness, headache, fatigue, bleeding
Cabar et al. 2007 [73]	Case report (poor)	Brazil (2007)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 72 *n* = 1 Age (years) = 28 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Carvajal et al. 2014 [68]	Prospective observational study (poor)	Spain (2011–2012)	Dose = ND *n* = 139 Age (years) = 26.2 ± 7.4 Exposure frequency = 1.0 ± 1.2 times Follow-up duration (years) = ND	NA	Menstrual disturbance; nausea, vomiting, diarrhea, dyspepsia, abdominal pain, stomatitis, and aphthous stomatitis; alteration of vaginal flow; headache or migraine; fatigue or asthenia; dizziness or vertigo; breast pain or swelling; vaginal bleeding; acne, skin disorders, and rash; miscarriage; ectopic pregnancy; unintended pregnancy; flushing, phlebitis, stroke, and thrombophlebitis, dysuria, lack of appetite, and porphyria; convulsions, antidiuretic hormone inadequate secretion, and herpes simplex, febrile neutropenia, and paresthesia

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Chen et al. 2011 [58]	Prospective observational study (fair)	Multicenter: China (2011)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 72 *n* = 2566 Age (years) = 27.4 ± 6.1 Exposure frequency = single dose Follow-up duration (hours) = 72	None	Nausea, vomiting, vaginal bleeding, headache and dizziness, xerostomia, transient chest distress, lower abdominal pain, anorexia, exanthema, fatigue, dizziness
Creinin et al. 2006 [48]	Randomized controlled trial (good)	Multicenter: USA (1999–2001)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 72 *n* = 774 Age (years) = 20–24 (mode) Exposure frequency = ND Follow-up duration (months) = ND	CDB-2914 *n* = 775 Age (years) = 20–24 (mode)	*Not significantly different:* Vomiting, headache, dizziness, fatigue, breast tenderness, lower abdominal pain, diarrhea, bleeding *Less in levonorgestrel:* Nausea, cycle range change
Dada et al. 2010 [53]	Clinical trial [RCT] (good)	Multicenter: Nigeria (2010)	Dose = 1.5 g, single dose; or 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 120 *n* = 1414 and 1409 in efficacy *n* = 1510 and 1512 in adverse events Age (years) = 26.4 ± 5.9 Exposure frequency = single dose Follow-up duration (weeks) = 1	NA	Nausea, fatigue, headache, dizziness, vomiting ($p > 0.05$)
Farajkhoda et al. 2009 [51]	RCT (poor)	Iran (2006–2007)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 72 *n* = 62 Age (years) = 26 ± 6 Exposure frequency = single dose Follow-up duration (cycle) = 1	Yuzpe regimen *n* = 60 Age (years) = 29 ± 7 Exposure frequency = single dose Follow-up duration (cycle) = 1	*Not significantly different:* Hot flash *Less in levonorgestrel:* Nausea, vomiting, headache, weakness

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Festin et al. 2016 [59]	Prospective observational study (poor)	Multicenter: Brazil, Thailand, Singapore and Hungary (2016)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 24 *n* = 330 Age (years) = 32.4 ± 6.8 Exposure frequency = more than once Follow-up duration (months) = 6.5	NA	Headache, nausea, abdominal and pelvic pain, influenza, acne vulgaris, candidiasis
Foer et al. 2016 [71]	Case series (good)	USA (2015)	Dose = ND *n* = 1 Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	NA	Hypersensitivity
Ghosh et al. 2009 [74]	Case report (fair)	India (2008)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 12 *n* = 1 Age (years) = 25 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Glasier et al. 2010 [60]	RCT [non-inferiority] (good)	Multicenter: UK, Ireland, and the USA (2010)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 120 *n* = 1117 Age (years) = 24.5 ± 6.1 Exposure frequency = single dose Follow-up duration (months) = ND	Ulipristal acetate 30 mg *n* = 1104 Age (years) = 24.9 ± 6.5 Exposure frequency = single dose Follow-up duration (months) = ND	*Not significantly different:* Headache, dizziness, *More in levonorgestrel:* Dysmenorrhea, abdominal pain *Less in levonorgestrel:* Nausea, fatigue, back pain

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Hamoda et al. 2004 [45]	RCT (fair)	UK (2001–2003)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 120 $n = 1021$ for efficacy; $n = 360$ for adverse event Age (years) = 23.0 ± 6.1 Exposure frequency = ND Follow-up duration (days) = 28–45	Mifepristone 10 mg $n = 1022$ for efficacy; $n = 360$ for adverse event Age (years) = 22 ± 5.7 Exposure frequency = ND Follow-up duration (days) = 28–45	*Not significantly different:* Nausea, vomiting, breast tenderness, abdominal pain, lethargy, headache, hot flushes, dizziness
Harper et al. 2004 [46]	Prospective observational study (good)	USA (2003)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus = ND $n = 52$ Age (years) = 15.5 ± 0.9 Exposure frequency = ND Follow-up duration (weeks) = 5	NA	Nausea, vomiting, dizziness, fatigue, headache, breast tenderness, lower abdominal pain, diarrhea
He et al. 1991 [40]	Clinical trial [RCT] (fair)	China (1990)	Dose = 0.75 mg, two doses Time between doses (hours) = 24 Time limit after coitus (hours) = 8 $n = 361$ Age (years) = 21–40 Exposure frequency (times) = 2–7 Follow-up duration (weeks) = 10	NA	Nausea, vomiting, dizziness, somnolence, leukorrhagia, lower abdominal pain, breast tenderness, fatigue
Ho and Kwan, 1993 [41]	RCT (fair)	China (1993)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 48 $n = 410$ Age (years) = 27.0 ± 6.4 Exposure frequency = ND Follow-up duration (weeks) = 6	Yuzpe regimen $n = 424$ Age (years) = 26.6 ± 6.7 Exposure frequency (times) = ND Follow-up duration (weeks) = 6	*Not significantly different:* Dizziness, breast tenderness, intermenstrual spotting/bleeding *Less in levonorgestrel:* Nausea, vomiting, fatigue

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Hoseini et al. 2013 [52]	RCT (fair)	Iran (2006–2007)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 72 *n* = 263 Age (years) = 28.8 ± 6.2 Exposure frequency = single dose Follow-up duration (weeks) = 1	Yuzpe regimen *n* = 266 Age (years) = 28.8 ± 5.6 Exposure frequency = single dose Follow-up duration (weeks) = 1	*Not significantly different:* Headache, fatigue, dizziness, breast tenderness, stomach pain, nose spot, diarrhea *Less in levonorgestrel:* Vomiting, nausea
Jian and Linan 2003 [75]	Case series (poor)	China (2003)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 8 and 72 *n* = 2 Age (years) = 26 and 35 Exposure frequency = single dose Follow-up duration (weeks) = ND	NA	Ectopic pregnancy
Kaymak et al. 2010 [76]	Case report (poor)	Turkey (2010)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 16 *n* = 1 Age (years) = 24 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Kesseru et al. 1973 [64]	Clinical trial (poor)	Peru (1973)	Dose = 0.15, 0.25, 0.30, 0.35 and 0.40 mg Time limit after coitus (hours) = 3 *n* = 4631 Age (years) = 28.7 [15–48] Exposure frequency = 5–13 times/month Follow-up duration (months) = 30	NA	Headaches, nervousness, abdominal pain, appearance or aggravation of chloasma, weight gain > 5 kg

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Kitani et al. 2019 [77]	Case report (fair)	Japan (2018)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 24 *n* = 1 Age (years) = 37 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Kozinszky et al. 2011 [78]	Case report (fair)	Norway 2010	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 5 *n* = 1 Age (years) = 27 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Lech et al. 2013 [54]	Prospective observational study (fair)	Poland (2004–2008)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 24 *n* = 4129 Age (years) = 22.4 ± 5.9 Exposure frequency = once Follow-up duration (weeks) = 4	NA	Headache, drowsiness, abdominal pain
Lerkiatbundit and Reanmongkol, 2000 [42]	Cross-sectional study (fair)	Thailand (1999)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 3 *n* = 100 Age (years) = 20–29 (mode) Exposure frequency (per month) = 1–4 Follow-up duration (months) = 12	NA	Menstrual cycle disturbance, dizziness, headache, nausea, vomiting, stomach ache

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Lomana et al. 2010 [70]	Case report (fair)	Spain (2010)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = ND *n* = 1 Age (years) = 22 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Venous thrombosis
Manzouri et al. 2015 [130]	Cross-sectional study (fair)	Iran (2012)	Dose = ND *n* = ND Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	Combined oral contraceptive pill *n* = ND Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	*Not significantly different:* Pregnancy, spotting and bleeding before next menstruation *Less in levonorgestrel:* Nausea, vomiting
Mittal et al. 2008 [61]	RCT (fair)	India (2008)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 120 *n* = 50 Age (years) = 28.8 ± 4.9 Exposure frequency = single dose Follow-up duration (days) = 31–49	Ormeloxifene 30 or 60 mg *n* = 47 and 49 Age (years) = 28.7 ± 6.1 and 27.9 ± 4.5 Exposure frequency = single dose Follow-up duration (days) = 31–49	*Not significantly different:* Nausea, fatigue, headache, breast tenderness, lower abdominal pain, weakness, delay of menses > 7 days *More in levonorgestrel:* Dizziness
Ngai et al. 2005 [47]	Clinical trial [RCT] (good)	China (1997–2003)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 or 24 Time limit after coitus (hours) = 72 *n* = 1027 and 1044 Age (years) = 27.1 ± 6.8 and 26.8 ± 6.7 Exposure frequency = single dose Follow-up duration (weeks) = 1	None	Nausea, vomiting, diarrhea, fatigue/weakness, dizziness, headache, breast tenderness[b], lower abdominal pain, delayed menses of more than 7 days[b], less frequent in the 24 h group ($p < 0.05$)

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Pereira et al. 2005 [79]	Case series (fair)	Brazil (2005)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = ND *n* = 2 Age (years) = 25 and 36 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy
Polakow-Farkash et al. 2013 [66]	Prospective cohort study (poor)	Israel (2005–2010)	Dose = ND *n* = 71 Age (years) = 30.5 ± 4.1 Exposure frequency = ND Follow-up duration (years) = 0.5–2	Desogestrel *n* = 72 Age (years) = 30.0 ± 4.5 Exposure frequency = every day Follow-up duration (years) = 0.5–2	*Not significantly different:* Dizziness *Less in levonorgestrel:* Maternal vaginal bleeding No reported adverse effects of levonorgestrel, during lactation, on feeding or behavior of the breastfeeding infant
Raine et al. 2012 [62]	Prospective observational study (good)	Multicenter, USA (2008–2010)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 72 *n* = 308 for efficacy *n* = 299 for adverse events Age (years) = 13–17 Exposure frequency = single dose Follow-up duration (weeks) = 8	NA	Headache, nausea, menstrual irregularity, pelvic pain, vaginal bleeding, vaginal spotting
Rani et al. 2017 [83]	Case report (fair)	India (2017)	Dose = 1.5 mg, single dose Time limit after coitus (hours) = 62 *n* = 1 Age (years) = 28 Exposure frequency = single dose Follow-up duration (months) = ND	NA	Ectopic pregnancy

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Raymond et al. 2006 [49]	Prospective observational study (good)	USA (2004–2005)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 24 *n* = 113 Age (years) = 20–25 (mode) Exposure frequency = ND Follow-up duration (weeks) = 9	Non-contraceptive drugs *n* = 843 Age (years) = 20–25 (mode) Exposure frequency = ND Follow-up duration (weeks) = 9	Intermenstrual bleeding following treatment is uncommon Other adverse effects: nausea, fatigue, abdominal pain, breast tenderness, headache and dizziness No participant reported vomiting or diarrhea
Santis et al. 2005 [65]	Retrospective cohort study (fair)	Telefono Rosso teratology information service, Italy (2000–2003)	Dose = ND *n* = 36 Age (years) = 30.2 (15–43) Exposure frequency = ND Follow-up duration = ND	Non-exposure *n* = 80 Age (years) = 30.8 (21–43) Exposure frequency = ND Follow-up duration = ND	*Not significantly different:* Preterm delivery, congenital anomalies, gastroesophageal reflux, monolateral nasolacrimal duct obstruction
Shaaban et al. 1984 [99]	RCT (fair)	Egypt (2010–2011)	Dose = 1.5 mg, single dose Time limit after coitus = 120 *n* = 579 Age (years) = 26.44 ± 5.58 Exposure frequency = single dose Follow-up duration (months) = 6	Lactation amenorrhea method *n* = 579 Age (years) = 25.90 ± 5.63 Exposure frequency = NA Follow-up duration (months) = 6	*More in levonorgestrel:* Nausea, vomiting
Sheffer-Mimouni et al. 2003 [80]	Case series (fair)	Israel (2002)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = ND *n* = 3 Age (years) = 19–34	NA	Ectopic pregnancy
Steele and Layman, 2016 [81]	Case report (fair)	USA (2016)	Dose = ND, single dose *n* = 1 Age (years) = 21 Exposure frequency = ND Follow-up duration (months) = ND	NA	Ectopic pregnancy

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Tan et al. 2004 [82]	Case report (fair)	Australia (2004)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 72 *n* = 1 Age (years) = 27 Exposure frequency = single dose Follow-up duration (weeks) = ND	NA	Ectopic pregnancy
Taylor et al. 2014 [55]	Prospective observational study (fair)	Multicenter: USA, Brazil (2010–2011)	Dose = 0.75 mg, single dose Time limit after coitus (hours) = 24 *n* = 72 Age (years) = 33 (14–45) Exposure frequency = ND Follow-up duration (months) = 6.5	NA	Anemia, vaginal candidiasis, headache, vaginal discharge, nausea, and upper respiratory tract infection
Tirelli et al. 2008 [50]	Prospective observational study (fair)	Italy (2005–2006)	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 24 *n* = 69 Age (years) = 24.0 ± 1.0 Exposure frequency = single dose Follow-up duration (weeks) = 10	NA	Spotting, nausea, headache
van Rooijen et al. 2007 [131]	Randomized crossover study (fair)	Sweden 2007	Dose = 0.75 mg, two doses Time between doses (hours) = 12 Time limit after coitus (hours) = NA *n* = 12 Age (years) = 21–34 Exposure frequency = single dose Follow-up duration (days) = 2	Ethinylestradiol 0.1 mg, and levonorgestrel 0.5 mg/tablet (two doses) *n* = 12 Age (years) = 21–34 (range) Exposure frequency = single dose Follow-up duration (days) = 2	Surrogate hemostasis marker Increased antithrombin, fibrinogen, free protein S, C-reactive protein, apoB/apoA1 Decreased activated factor VII (FVIIa), sex hormone-binding globulin

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Task Force on Post-Ovulatory Methods for Fertility Regulation, 2000 [132]	Prospective observational study (fair)	Multicenter: China, Cuba, Pakistan, Russia Slovenia (2000)	Dose = 0.75 mg, single-dose or two doses Time between doses (hours) = 12 Time limit after coitus (hours) = 1 *n* = 295 Age (years) = 32.9 ± 6.4 Exposure frequency = ND Follow-up duration (months) = 6	NA	Intermenstrual bleeding, nausea, breast tenderness, weakness, dizziness, headache, abdominal bloating or pain, loss of libido, depression and vomiting
von Hertzen et al. 2002 [44]	RCT (good)	Multicenter: China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, and the UK (2002)	Dose = 1.5 mg single dose, or two doses of 0.75 mg Time between doses (hours) = 12 Time limit after coitus (hours) = 120 *n* = 1379 + 1377 Age (years) = 27.1 ± 7.2 and 27.4 ± 7.1 Exposure frequency = single dose Follow-up duration (weeks) = 1	Mifepristone 10 mg *n* = 1380 Age (years) = 27.2 ± 7.0 Exposure frequency = single dose Follow-up duration (weeks) = 1	*Not significantly different:* Nausea, vomiting, diarrhea, fatigue, dizziness, headache, breast tenderness, lower abdominal pain *More in levonorgestrel:* Bleeding *Less in levonorgestrel:* Delayed menses of > 7 days
Zhang et al. 2015 [13]	Prospective cohort study (good)	China (1999–2008)	Dose = < 1.5 mg or > 1.5 mg *n* = 191 Age (years) = 27.7 ± 3.2 Exposure frequency = ND Follow-up duration (years) = 1	Healthy pregnant women *n* = 211 Age (years) = 28.2 ± 2.9 Exposure frequency = NA Follow-up duration (years) = 1	Levonorgestrel has no effect on physical and mental development of children born after contraception failure
Bondon-Guitton et al. 2012[a] [125]	Case series	French Pharmacovigilance System (1984–2010)	Dose = ND *n* = ND Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	NA	Gingival overgrowth
Brinker and Beitz, 2002[a] [126]	Case series	Adverse Events Reports System, USA (2000)	*n* = ND Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	NA	Impaired wound healing

Table 1 (continued)

Study or reference	Study design, for safety outcome (quality)	Location (year of study)	Levonorgestrel group	Control group	Reported adverse effects
Buccellato et al. 2013[a] [127]	Case series	WHO Global ICSRs database (1972-2012)	Dose = ND *n* = 546 Age (years) = ND Exposure frequency = ND Follow-up duration (hours) = ND	NA	Paresthesia
Kurian et al. 2018[a] [15]	Case series	Drug Administration FAERS Database, USA (2006–2015)	Dose = ND *n* = ND Age (years) = ND Exposure frequency = ND Follow-up duration (months) = ND	NA	Breast enlargement, breast tenderness, dysmenorrhea, ectopic pregnancy, menorrhagia, menstruation delayed, metrorrhagia, nipple disorder, pregnancy, premenstrual syndrome, diarrhea, dysuria, fungal infection, muscle spasm, pollakiuria

Age is expressed as mean ± SD, median (range), or range unless specified otherwise

RCT randomized controlled trial, *ND* no data, *NA* not applicable, *ICSRs* individual case safety reports, *WHO* World Health Organization, *FAERS* US FDA Adverse Event Reporting System, *SD* standard deviation, *apo* apolipoprotein

[a]Studies were not included in the systematic review because there was possibility that levonorgestrel not used as an emergency oral contraceptive was included in these studies. They are shown in this table as they have been mentioned in the "Discussion" section of this article

Table 2 Pooled prevalence of adverse reactions during the use of the levonorgestrel emergency oral contraceptive

Adverse reaction	No. of studies	Pooled estimate, as a percentage (95% CI)	Event/total	I^2
Gynecological adverse reactions				
Breast pain	16	8.3 (5.8–10.7)	730/10,488	98.0
0.75 mg	12	10.1 (6.8–13.3)	607/6319	97.0
1.50 mg	3	3.4 (−1.9 to 8.7)[a]	117/4030	98.2
Late menstruation	7	6.5 (4.7–8.4)	306/5336	85.4
0.75 mg	5	7.6 (4.9–10.2)	229/3827	90.2
1.50 mg	2	5.1 (4.0–6.2)	77/1509	00.0
Vaginal spotting	6	4.9 (2.5–7.4)	129/3873	87.2
Intermenstruation spotting	5	23.5 (7.8–39.2)	330/1462	98.5
Pelvic pain	3	11.1 (2.4–19.8)	223/1746	97.3
Alteration of menstrual flow	1	46.8 (38.5–55.1)	65/139	NA
Amenorrhea	1	13.0 (6.4–19.6)	13/100	NA
Candidiasis	2	0.79 (5.3–10.6)	32/402	0.00
Cervical dysplasia	1	1.4 (−1.3 to 4.1)[a]	1/72	NA
Cycle range change	1	2.1 (1.1–3.1)	16/774	NA
Early menstruation	2	18.5 (5.1–32.0)	62/395	88.0
Hot flash	2	9.2 (−2.4 to 20.7)[a]	56/442	93.8
Hypermenorrhea	2	13.7 (10.3–17.1)	54/395	0.00
Hypomenorrhea	2	26.2 (21.9–30.6)	104/395	0.00
Longer menstruation	1	13.2 (9.4–17.1)	32/295	NA
Menorrhagia	1	15.6 (12.6–18.7)	85/544	NA
Menstrual disturbance	2	11.1 (−7.3 to 29.6)[a]	35/438	96.5
Premenstrual spotting/bleeding	1	9.9 (7.4–12.4)	54/544	NA
Prolonged spotting/bleeding	1	3.1 (1.7–4.6)	17/544	NA
Shorter menstruation	1	13.6 (9.7–17.5)	40/295	NA
Vaginal discharge/leukorrhagia	2	2.4 (1.0–3.8)	11/433	0.00
Neurological adverse reactions				
Headache	24	12.4 (9.8–14.9)	1764/18,917	98.6
0.75 mg	16	13.0 (9.8–16.2)	1098/11,492	97.7
1.50 mg	8	11.4 (5.6–17.3)	650/7425	99.0
Dizziness	21	10.8 (8.7–12.9)	1388/16,406	96.3
0.75 mg	15	12.4 (9.6–15.3)	1015/12,060	97.0
1.50 mg	4	8.6 (5.5–11.8)	359/4136	91.8
Depression	1	2.4 (0.6–4.1)	7/275	NA
Loss of libido	1	5.1 (2.6–7.6)	15/295	NA
Somnolence	1	3.0 (1.3–4.8)	11/361	NA
Gastrointestinal tract adverse reactions				
Nausea	25	15.0 (11.9–18.1)	2271/15,999	97.5
0.75 mg	17	15.4 (11.7–19.2)	1266/8134	96.2
1.50 mg	8	14.1 (8.3–19.9)	1005/7865	98.5
Vomiting	20	8.5 (−4.7 to 21.7)[a]	710/14,506	99.9
0.75 mg	15	10.0 (−11.6 to 31.6)	503/7993	99.9
1.50 mg	5	3.9 (1.7–6.1)	207/6513	98.0
Lower abdominal pain	17	11.4 (8.8–14.0)	1255/15,285	98.9
0.75 mg	13	13.5 (9.5–17.5)	936/10,138	98.4
1.50 mg	4	6.7 (−0.7 to 14.1)[a]	319/5147	99.1
Diarrhea	7	4.4 (2.4–6.4)	243/5941	97.5
0.75 mg	6	4.5 (2.4–6.6)	189/4582	97.4
1.50 mg	1	4.0 (2.9–5.0)	54/1359	NA

Table 2 (continued)

Adverse reaction	No. of studies	Pooled estimate, as a percentage (95% CI)	Event/total	I^2
Abdominal bloating	1	7.5 (4.5–10.5)	22/295	NA
Xerostomia	2	7.0 (−7.7 to 21.7)[a]	16/2573	88.9
Anorexia	1	0.1 (−0.0 to 0.3)[a]	3/2521	NA
Miscellaneous adverse reactions				
Fatigue	19	14.0 (10.3–17.8)	1658/14,430	99.1
0.75 mg	13	17.5 (12.3–22.8)	1219/7634	98.3
1.50 mg	5	6.8 (1.3–12.3)	426/6657	99.1
Dermatological adverse events	5	1.0 (0.3–1.6)	94/7884	96.5
Anemia	1	15.3 (7.0–23.6)	11/72	NA
Back pain	1	2.4 (1.5–3.3)	27/1117	NA
Bleeding	2	31.0 (29.3–32.7)	843/2720	00.0
Stroke	1	0.4 (−0.6 to 1.3)[a]	0/139	NA
Upper URI	2	5.6 (0.3–10.9)	29/402	79.4
Weight gain	1	0.1 (0.0–0.2)	5/4631	NA
Pregnancy and neonatal complications				
Pregnancy rate	26	1.7 (1.3–2.1)	305/18,028	79.4
0.75 mg	16	1.5 (1.0–2.0)	175/11,929	73.0
1.50 mg	9	1.9 (1.1–2.7)	112/5906	83.3
Congenital anomalies	1	4.0 (−3.7 to 11.7)[a]	1/25	NA
Ectopic pregnancy	1	0.4 (−0.6 to 1.3)[a]	0/139	NA
Miscarriage	1	0.4 (−0.6 to 1.3)[a]	0/139	NA
Neonatal complications	2	2.6 (−0.7 to 6.0)[a]	6/216	12.5
Preterm delivery	1	4.0 (−3.7 to 11.7)[a]	1/25	NA

CI confidence interval, *URI* upper respiratory infection, *NA* not applicable

[a]Denotes the percentage of pooled estimates that were not significantly different from zero ($p > 0.05$)

$n = 25$, $I^2 = 97.5\%$), vomiting (8.5%; 95% CI −4.7 to 21.7%; $n = 20$, $I^2 = 99.9\%$), lower abdominal pain (11.4%; 95% CI 8.8–14.0%; $n = 17$, $I^2 = 98.9\%$), and diarrhea (4.4%; 95% CI 2.4–6.4%; $n = 7$, $I^2 = 97.5\%$), while miscellaneous outcomes included fatigue (14.0%; 95% CI 10.3–17.8%; $n = 19$, $I^2 = 99.1$). After analysis by stratifying the data by the dose of levonorgestrel, the prevalence of these aforementioned outcomes in users receiving a levonorgestrel 0.75 mg two-dose regimen and users receiving a levonorgestrel 1.5 mg single-dose regimen were not statistically different ($p > 0.05$) [Table 3].

3.3 Levonorgestrel Emergency Oral Contraceptives and Pregnancy Outcomes

This systematic review found two studies that reported pregnancy outcomes after failure of the levonorgestrel contraceptive. De Santis et al. found that the rate of preterm delivery and congenital anomalies (e.g. gastroesophageal reflux and monolateral nasolacrimal duct obstruction) in levonorgestrel users and non-users was not significantly different [65]. In addition, Zhang et al. found that levonorgestrel had no effect on the physical and mental development of children born after failure of the contraceptive [67]. Levonorgestrel had no adverse effects on the feeding or behavior of breastfeeding infants [66]. Moreover, 11 case reports documented ectopic pregnancy after the use of levonorgestrel emergency oral contraceptives [72–83]. In every case report, ectopic pregnancy occurred after the use of levonorgestrel. Most of the studies did not report concomitant drug use in patients, except for the work of Cabar et al., which reported no concomitant drug use [73], and Tan et al., which reported that an IUD was inserted concomitantly with the use of oral levonorgestrel [82]. Only two studies reported on the previous abortion status of patients [79, 81], and four studies reported the status of the previous infection in the reproductive system [79–81, 83].

The pooled pregnancy rate after the use of levonorgestrel contraception from this meta-analysis was 1.7% (95% CI 1.3–2.1%; $n = 26$, $I^2 = 79.4\%$). The rate of pregnancy was not statistically different between the 0.75 mg two-dose regimen (1.5%, 95% CI 1.0–2.0%; $n = 16$, $I^2 = 73.0\%$) and the

Table 3 Adverse events of levonorgestrel emergency oral contraceptive reported in the FAERS database

Type of adverse events	Non-serious adverse events [$n=114$]		Serious adverse events [$n=66$]	
	N (%)	Examples	*N* (%)	Examples
Gynecological	64 (56.1)	Bloody discharge, breast pain, breast tenderness, menstruation irregular, dysmenorrhea, vaginal hemorrhage	2 (3.0)	Ovarian cyst ruptured, ovarian disorder
Neurological	4 (3.5)	Dizziness, headache	0	–
Gastrointestinal	21 (18.4)	Nausea, vomiting, abdominal pain, increase appetite	3 (4.5)	Abdominal hernia, appendicitis
Pregnancy and complications	0	NA	36 (54.5)	Spontaneous abortion, ectopic pregnancy, pregnancy
Anaphylaxis and other allergic reactions	0	NA	6 (9.1)	Anaphylactic reaction, urticaria, systemic lupus erythematosus
Cancer	0	NA	2 (3.0)	Lung neoplasm, cervix carcinoma
Infection	2 (1.8)	Nasopharyngitis	5 (7.5)	Urinary tract infection, bacterial vulvovaginitis, pneumonia, pericarditis
Psychiatric	7 (6.1)	Crying, mood swing	6 (9.1)	Anxiety, hallucination, suicidal ideation
Cardiovascular	1 (0.9)	Increased heart rate	5 (7.5)	Unilateral blindness (retinal vein thrombosis), pulmonary embolism, thrombosis
Musculoskeletal	0	NA	1 (1.5)	Musculoskeletal stiffness, pain
Others	15 (13.2)	Rash, pruritus, inappropriate schedule of product administration, intentional product misuse	0	NA

FAERS US FDA Adverse Event Reporting System, *NA* not applicable

1.50 mg single-dose regimen (1.9%, 95% CI 1.1–2.7%; $n=9$, $I^2=83.3\%$). The prevalence of miscarriage, ectopic pregnancy, preterm delivery, congenital anomalies, and neonatal complications were not significantly different from zero ($p>0.05$) [Table 3].

3.4 Descriptive Data from the US FDA Adverse Events Reporting System (FAERS) Database

As of 1 February 2020, 247 cases that reported adverse events during the use of levonorgestrel oral emergency contraception were retrieved from the FAERS database. Of these reports, 51 cases reported levonorgestrel use with other concurrent active ingredients or medication, and 16 cases reported problems with contraceptive devices, and hence were further excluded. From the remaining 180 cases, there were 66 serious adverse events, including one death from a pulmonary embolism and one unilateral blindness from retinal vein thrombosis, and 114 non-serious adverse events. An illustration of these cases is shown in Table 3. Ectopic pregnancy was the only serious adverse event that was both reported in the FAERS database and found during the systematic review. In other words, convulsion, febrile neutropenia, and stroke, which were found during the systematic review, were not found in the FAERS database. Other serious adverse events reported in the database included abdominal hernia, anaphylactic reaction, cancer ovarian, cyst rupture, embolism (retinal vein thromboembolism resulting in unilateral blindness, and pulmonary embolism resulting in death), serious infections, and suicidal ideation (Table 3).

4 Discussion

Despite the fact that levonorgestrel is effective and well tolerated as an emergency oral contraceptive, myths about its safety discourage the use of levonorgestrel in patients. The situation is complicated by the political and religious perspective of using oral contraceptives [84, 85]. This study is the first to summarize the evidence regarding the prevalence of adverse reactions related to levonorgestrel oral contraceptives. We aimed to emphasize the safety of the levonorgestrel method of contraception. The results from this meta-analysis showed that the most common, and common, adverse effects of levonorgestrel were not serious. The prescribing information of Plan B One-Step deposited in the US FDA database demonstrates that the most common adverse reactions (≥ 10%) of levonorgestrel emergency oral contraceptives in clinical trials included heavier menstrual bleeding (31%), nausea (14%), lower abdominal pain (13%), fatigue (13%), headache (10%), and dizziness (10%) [86]. This

meta-analysis showed that the rate of nausea (15%), lower abdominal pain (11.4%), fatigue (14%), headache (12.4%), and dizziness (10.8%) approximated to the rate reported in the prescribing information; however, the meta-analysis was not able to show the rate of bleeding because of variation in the terminology that was used in each included article.

In this systematic review, multiple serious adverse events were found, including convulsion, ectopic pregnancy, febrile neutropenia, stroke, abdominal hernia, anaphylactic reaction, cancer, ovarian cyst rupture, serious infections, and suicidal ideation. The biological plausibility of each adverse event is discussed. Progesterone has antiseizure effects with an undefined mechanism of action [87]; however, it is possible the levonorgestrel induces seizure because the withdrawal of progesterone results in convulsion [88, 89]. For ectopic pregnancy, several observational studies support that the use of levonorgestrel is associated with it [13–15, 90]. A possible mechanism for levonorgestrel-induced ectopic pregnancy may be the reduction in ciliary beat frequency [91]. Next, a meta-analysis published in 2009 supports that progestogen-only contraceptives are not associated with the risk of stroke [92]. In addition, several studies confirmed that the risk of venous thrombosis in levonorgestrel users is lower than other progestogens [93–96]. However, some studies suggest an association between levonorgestrel and stroke [97, 98]. Together with the fact that levonorgestrel still involves the coagulation cascade, e.g. factors II, VII, X, and fibrinogen [99, 100], coagulation-relevant adverse reactions such as embolism and stroke are biologically plausible.

Regarding the risk of cancer, plenty of studies investigated the association between levonorgestrel and breast cancer. This is biologically plausible because in vitro studies show that progestogens play important roles in the proliferation of breast cancer [101–103]; however, such an association still requires investigation since observational studies in humans found conflicting results on the association between levonorgestrel and breast cancer [104, 105]. In this study, the incidence of lung and cervical cancer was identified. Although studies on the mechanism of levonorgestrel are not available, the study by Soini et al. shows a decrease in the risk of lung cancer in levonorgestrel users [104]. In addition, the study by Averbach et al. associates the risk of cervical cancer with levonorgestrel IUDs [106]; however, this association stems from the use of IUDs since the devices can disrupt the cervical cytology [107]. Together with several in vivo studies indicating that progestin has anticervical cancer effects [108–110], the positive association between cervical cancer and oral levonorgestrel is very unlikely.

This systematic review also found cases of infections during the use of levonorgestrel. The use of emergency contraception raises concerns about the increase in the rate of sexually transmitted disease (STD), but several studies have shown that the use of emergency contraceptive pills is not associated with the risk of STDs [111, 112]. However, evidence shows that progesterone-based compounds reduce the numbers of CD8 + T cells and lower secretion of proinflammatory cytokines [113, 114]. The effect of the compounds may alleviate or aggravate the infections, depending on the type of pathogens; therefore, there is a possibility that the use of levonorgestrel is associated with increased susceptibility in infections other than STDs.

Another incidence type identified as a result of this systematic review was psychiatric events. The use of progestins is associated with anxiety [115], depression [115–117], psychiatric disorders [118], and suicidal attempts [119]. Although the exact mechanism is unknown, it is possible that progesterone may cause such adverse effects because progesterone receptors are expressed wildly in the brain, including in the hippocampus and frontal cortex [120], i.e. the parts responsible for memory, emotion, cognition, and behavior [121, 122]. The possible mechanisms that explain the association between the use of levonorgestrel and abdominal hernia, febrile neutropenia, and ovarian cyst rupture are currently unavailable.

There were some limitations to this meta-analysis. First, the included studies were conducted in different countries around the globe and the methodology of the studies was varied. As a result, pooled statistics from the meta-analysis demonstrated high heterogeneity, which might have complicated the interpretation of the results. However, there was no attempt to categorize the study according to study location, design or quality because the number of publications per adverse reaction was small. The diversity in the dosing regimen, dosing schedule, and study design could be the reasons for heterogeneity. Second, this systematic review and meta-analysis included only studies that investigated the adverse reactions of levonorgestrel emergency contraceptives that are used orally. The rationale for the inclusion criteria was that there are studies showing that delivery systems such as IUDs [123] or transdermal delivery systems [124] are related to ectopic pregnancy and contact dermatitis, respectively. In addition, adverse reactions reported by studies using levonorgestrel as progestin-only pills can be long-term toxicities that are not related to the nature of the short-term sporadic use of levonorgestrel emergency contraceptives; however, because of this rationale, we decided to exclude multiple studies that may have included daily use of levonorgestrel [15, 125–127], or studies that included combined oral contraceptives that associated levonorgestrel with several adverse reactions e.g. cardiovascular death [128], depression [117], gallbladder disease [129], and venous thromboembolism [18, 21].

Next, most of the included studies were designed to study the contraceptive efficacy of levonorgestrel. Safety outcomes were mostly not the primary outcome; therefore, statistical

analysis in the included studies might have had less power to detect the statistical difference among levonorgestrel users and non-users. This was overcome by pooling the data from each study and meta-analyzing the adverse reactions regardless of the differences in the comparators. In addition, the association between adverse effects and levonorgestrel reported in observational studies that were used in this meta-analysis does not equate to the causal relationship between levonorgestrel and the adverse effects.

Last, the results from the meta-analysis of the pregnancy rates was biased by the search criteria. Several studies recommended other contraception as back-up methods [44, 47, 53, 54, 59, 63]. Data from some studies could not be included in the meta-analysis because the studies were designed to capture the failure rate of contraception [65]. This was anticipated since the primary outcome of this systematic review was adverse reactions, not the efficacy of the oral contraceptives. Hence, the pregnancy rate from this meta-analysis must be interpreted with caution.

This study provides extensive safety data on levonorgestrel emergency oral contraception. For research perspectives, multiple signals for uncommon or serious adverse reactions, e.g. chloasma, convulsion, ectopic pregnancy, exanthema, febrile neutropenia, miscarriage, stroke, and venous thrombosis, were revealed from the literature search. This can be used as an hypothesis for further observational studies or systematic reviews and meta-analyses to prove whether the incidence was associated with the use of levonorgestrel. In fact, several observational studies have been conducted to find the association between ectopic pregnancy and levonorgestrel [13–15]. In addition, this systematic review shows that data on the adverse reactions of repeated use of levonorgestrel are scarce. Studies on the multiple uses of levonorgestrel emergency contraception are still required to ensure the safety of levonorgestrel emergency contraception.

The results of this systematic review and meta-analysis have several clinical meanings. First, the prevalence of the serious adverse reactions of levonorgestrel emergency contraception was not common and not statistically significant. Common adverse reactions were not serious and included menstruation disturbances, headache, dizziness, nausea, vomiting, abdominal pain, diarrhea, and fatigue. Therefore, the use of levonorgestrel emergency oral contraceptives should be promoted in populations that are in need but who also have safety concerns. The prevalence of adverse reactions in the levonorgestrel 0.75 mg two-dose regimen group and the levonorgestrel 1.5 mg single-dose regimen group were not statistically different. This finding reveals the possibility of flexible dosing schedules of levonorgestrel. However, the clinical implications of this study are confounded by the limitations based on the quality of the included studies. To improve the quality of the literature regarding adverse reactions from levonorgestrel, reporting guidelines should be compiled to enable the scientific community to clearly evaluate the study. The use of medical dictionary terminology for reporting adverse events during studies will greatly improve the feasibility of pooling data into a meta-analysis. Additional large observational studies with a low risk of selection bias, and postmarketing surveillance designed to detect the adverse effects of levonorgestrel, specifically used as emergency oral contraceptives, are needed to ascertain the safety of levonorgestrel used as an emergency oral contraceptive.

5 Conclusions

This systematic review and meta-analysis found that most of the adverse reactions of oral levonorgestrel for emergency contraception were common and not serious. Serious adverse reactions identified included convulsion, ectopic pregnancy, febrile neutropenia, and stroke. Ectopic pregnancy was the only serious adverse event identified from both systematic reviews and FAERS reports. The use of a 0.75 mg two-dose regimen and a 1.50 mg single-dose regimen showed no difference in the prevalence of adverse effects and the rate of pregnancy. To ascertain the safety of levonorgestrel used as an emergency oral contraceptive, both in the short- and long-term, additional large observational studies with a low risk of selection bias, and postmarketing surveillance designed to detect the adverse effects of levonorgestrel specifically used as an emergency oral contraceptive, are needed.

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Compliance with Ethical Standards

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