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Safety data for levonorgestrel, ulipristal acetate and Yuzpe regimens for emergency contraception

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Abstract

The World Health Organization (WHO) and the US Centers for Disease Control and Prevention (CDC) provide recommendations for use of emergency contraceptive pills (ECPs), including levonorgestrel (LNG) and combined oral contraceptives (COCs). A new ECP formulation, ulipristal acetate (UPA), is now available worldwide. To determine whether LNG, UPA or COC (Yuzpe) ECPs are safe for women with certain characteristics or medical conditions, we searched the PubMed and Cochrane databases for articles published from date of inception until May 2015 pertaining to the safety of LNG, UPA or Yuzpe ECP use. For direct evidence, we considered studies that looked at safety outcomes among women with certain medical conditions or characteristics taking ECPs compared with women not taking ECPs. For indirect evidence, we considered studies that reported pharmacokinetic (PK) data for ECP use among women with certain medical conditions or characteristics and studies that reported safety outcomes among healthy women taking ECPs. Five studies provided direct evidence; of these five studies, four examined LNG or Yuzpe use among pregnant or breastfeeding women, and one reported risk of ectopic pregnancy among women repeatedly using LNG ECPs. Poor pregnancy outcomes were rare among pregnant women who used LNG or Yuzpe ECPs during the conception cycle or early pregnancy. Breastfeeding outcomes did not differ between women exposed to LNG ECP and those unexposed, and there was no increased risk of ectopic pregnancy versus intrauterine pregnancy after repeated use of LNG ECPs compared with nonuse. Forty-five studies provided indirect evidence. One PK study demonstrated that LNG passes into breastmilk but in minimal quantities. In addition, nine studies examined pregnancy outcomes following ECP failure among healthy women, and 35 articles reported adverse events. Studies suggest that serious adverse events are rare among women taking any of these ECP formulations. Implications: Evidence on safety of ECPs among women with characteristics or medical conditions listed within WHO and CDC family planning guidance is limited. However, both direct and indirect evidence for our study question did not suggest any special safety concerns for the use of ECPs among women with particular medical conditions or personal characteristics, such as pregnancy, lactation or frequent ECP use. Published by Elsevier Inc.

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Conflicts of Interest: none.

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Keywords

Emergency contraceptive pills; Ulipristal; Levonorgestrel; Yuzpe; Safety

1. Introduction

Emergency contraceptive pills (ECPs) offer women and couples pregnancy prevention after unprotected sexual intercourse, or incorrect or inconsistent use of contraception. Globally, three types of ECPs are widely available: a combined oral contraceptive (COC) pill regimen (referred to as the *Yuzpe* regimen); a 1.5-mg dose of the progestogen levonorgestrel (LNG), taken either in one dose or split doses 12 h apart, and a more recently introduced medication, ulipristal acetate (UPA) at a dose of 30 mg [1]. While all three ECP formulations are safe, providers may be concerned about their use among women with certain medical conditions or personal characteristics. The duration of ECP exposure for one or two doses is less than that of ongoing use of hormonal contraception and thus would be expected to have less risk of adverse events (AEs).

We conducted this systematic review initially in preparation for an expert working group consultation of international family planning experts convened by the World Health Organization (WHO) in September 2014 to review WHO evidence-based contraceptive guidance; we then updated this systematic review in preparation for a meeting to discuss Centers for Disease Control and Prevention (CDC) evidence-based contraceptive guidance for the United States in August 2015. The objective of this review was to determine from the literature whether use of ECPs among women with certain characteristics or medical conditions is associated with increased risk of adverse outcomes compared with women who do not use these methods. We also summarized studies that provided indirect evidence for these recommendations, including PK data among women with certain characteristics or medical conditions or safety data among healthy women.

2. Materials and methods

We conducted this review according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [2]. We searched PubMed from database inception through May 2015, using the search strategy in Appendix A. We also searched the Cochrane Library from inception through May 2015 using the basic search term *emergency contraception* (EC). We hand searched review articles for any pertinent references and reviewed ECP labeling information for any published safety reports. We did not attempt to identify unpublished articles or abstracts from scientific conferences.

2.1. Selection criteria

We included direct evidence, defined as primary research articles in all languages that reported AEs or safety outcomes following ECP use (LNG, UPA or Yuzpe regimens) among women with specific characteristics or medical conditions, as listed in the ECP chapter within the WHO Medical Eligibility Criteria for Contraceptive Use (MEC), and included a comparison of women with the same conditions or characteristics who did not use ECPs.

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These conditions and characteristics included: pregnancy, breastfeeding (BF), past ectopic pregnancy, history of severe cardiovascular complications, angina pectoris, migraine, severe liver disease, repeated ECP use and rape [3]; we also considered the additional characteristics or medical conditions for ECPs listed in the CDC US MEC, including history of bariatric surgery, rheumatoid arthritis, inflammatory bowel disease and solid organ transplantation [4]. We did not include ECPs for which WHO or CDC does not provide recommendations, for example, mifepristone. We did not include drug interactions as a condition, as this evidence is included in a separate forthcoming systematic review. We did not consider common side effects of these formulations (e.g., nausea and vomiting) as outcomes of interest.

Since we found few primary articles that directly answered our research question, we broadened our search to include reports that provided indirect evidence relevant to our study question. For indirect evidence, we included studies of indirect outcomes (e.g., PK outcomes, rather than clinical outcomes, among women with medical conditions or characteristics of interest to us), studies with indirect study populations (e.g., healthy, nonpregnant women rather than women with specific characteristics or medical conditions) and studies of healthy women without a direct comparison group (e.g., studies that reported pregnancy outcomes after EC failure from efficacy trials that did not include a non-ECP comparison group).

For studies that reported AEs among healthy women, we excluded studies that did not investigate or report the timing of ECP use in relation to the reported AE. We excluded studies that reported on the occurrence of pregnancies but did not include outcomes for all pregnancies. We did not include PK studies that examined ECP use among healthy women without any conditions or characteristics included in either WHO or US MEC. We did not include articles on the use of UPA for treatment of fibroids, as the dose is much lower than that used for EC. We did not include articles on the planned use of these contraceptive formulations for pericoital contraception, which involves taking multiple doses of pills each month for regular contraception, with doses immediately before and/or after every act of intercourse.

2.2. Study quality assessment and data synthesis

Two authors summarized and systematically assessed the evidence through the use of standard abstract forms (TCJ and HR) [5]. We assessed the quality of each study with direct evidence using the United States Preventive Services Task Force grading system [6]. We did not grade the quality of the indirect evidence. Due to heterogeneity among studies identified, we did not compute summary measures of association.

3. Results

This search identified 3786 articles. Most studies identified with our search strategy were excluded because they examined oral contraceptive pill (OCP) use for regular contraception rather than ECP use or because they examined ECP use (e.g., effectiveness) but did not report safety outcomes. Several additional studies examined regular pericoital use of these formulations; these were also excluded.

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Five studies fit the inclusion criteria for direct evidence evaluating the safety of ECP use among women with certain characteristics or medical conditions of interest compared with women with these characteristics or conditions not using ECPs [4,7–10] (Table 1). Two of these studies examined LNG ECP use among BF women [7,8]. Two studies examined ECP use among pregnant women [9,10]; one of these looked at LNG ECP use alone [10], and one examined use of both LNG ECPs and Yuzpe among pregnant women [9]. One study examined repeated use of LNG ECPs compared with nonuse and reported the odds of ectopic pregnancy versus intrauterine pregnancy (IUP) [4]. We did not identify any studies that examined Yuzpe alone or UPA use among these populations.

For indirect evidence, we identified one PK study examining LNG ECP use among BF women [11] (Table 2). We also identified several studies among healthy women. Of these, nine studies examined ECP use among healthy women without a non-ECP comparison group and reported pregnancy outcomes for EC failures [12–20] (Table 2). Thirty-five studies reported AEs among healthy women taking ECPs [14,18,20–52] (data not shown in tables).

3.1. Direct evidence: studies among women with specific characteristics or medical conditions

3.1.1. ECP use among pregnant women—One prospective cohort study examined pregnant women who took ECPs during the conception cycle, and one retrospective cohort study examined pregnant women who took ECPs during the first trimester. The prospective cohort study recruited pregnant women from Chinese prenatal clinics and compared 332 women who took LNG ECPs during their conception cycle with 332 women who did not take LNG, matched by date of birth (DOB) and last menstrual period (LMP) [10]. There were no differences in first trimester miscarriages or congenital malformations (either on ultrasound or at delivery) between groups. Second trimester terminations occurred in each group for fetal malformations; one case of congenital polycystic kidney was diagnosed in the exposed group and one case of sacrococcygeal tumor and one case of achondroplasia were diagnosed in the unexposed groups. The retrospective cohort study recruited 36 pregnant women who contacted a teratology information service in Italy after taking either Yuzpe (n=11) or LNG ECPs (n=25) in the first trimester and compared them with 80 pregnant women calling about exposure to other nonteratogenic drugs [9]. Timing of exposure to ECPs ranged from day 10 to 45 of pregnancy. There were no significant differences found in the ECP exposed group compared with the unexposed group for rates of spontaneous abortion (6/36 vs. 3/80) or stillbirths (0/36 vs. 1/80). No maternal complications were reported in either group, and there were no differences in neonatal weight, length or risk of malformations.

3.1.2. ECP use among BF women—One prospective cohort study reported effects of LNG during BF on infant and mother outcomes and milk volume. This study recruited 71 BF women in Israel who contacted a teratology information service telephone line regarding LNG EC use and compared them with a control group of 72 BF women calling for information about ethynodiol diacetate or desogestrel use [7]. No adverse effects were reported on feeding or infant behavior outcomes in the LNG group, while two infants in

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control group were noted to have transient irritability and one infant in control group was diagnosed with hypertrichosis. One infant in LNG-exposed group was reported to have weight less than fifth percentile at 1 year, and one infant in non-LNG-exposed group was reported to have "slow development" at 1 year. There were no differences in subjective estimates of milk volume between the two groups. Of those who took LNG, the majority of women (75%) discontinued BF for less than 8 h, while the rest discontinued for greater than 8 h before reinitiating. Two women of 71 (2.8%) who took LNG did not reinitiate BF.

An open-label trial randomized 1158 women intending to use lactational amenorrhea method (LAM) for 6 months and breastfeed for 1 year into one of two groups: either standard postpartum contraceptive counseling, plus counseling on and advance provision of LNG EC, or standard postpartum contraceptive counseling alone [8]. The authors reported no difference in the duration of lactation, resumption of menstruation or pattern of BF between the two groups. Of those subjects randomized to EC counseling and advance provision, 44% actually took the ECPs, and these women did not report any changes over time in milk quantity or infant health; other outcomes were not reported in further detail for women who actually took the ECPs.

3.1.3. Repeated LNG ECP use—One case control study from China identified 2411 cases of ectopic pregnancy and 2419 controls with intrauterine pregnancies matched by age, marital status and gestational age [4]. Participants were interviewed with the focus on previous and current use of LNG ECPs. The study compared repeated use of ECPs within the last year (1–2, 3–4 or 5 or more times) with nonuse and found no increased odds for ectopic pregnancy versus IUP and no significant increasing trend for odds of ectopic pregnancy with increasing use categories (p=0.67).

3.2. Indirect evidence

3.2.1. PK studies among women with specific characteristics or medical conditions—One PK study provided indirect evidence for the use of LNG ECPs among BF women (Table 2). This study examined 12 exclusively BF healthy women who were given one dose of LNG ECPs. The authors assessed venous and milk samples for levels of LNG and sex hormone binding globulin (SHBG) for 120 h [11]. Subjects abstained from nursing for 72 h after dosing and provided infants with milk previously pumped and frozen; no samples were collected from infants. No serious AEs were reported among women or infants that were related to drug intake. The half-life of LNG in breast milk was found to be 26.3 h with a peak levels between 2 and 4 h. Maximum calculated infant exposure was estimated to be 1.6 mcg between 0 and 24 h.

3.2.2. Studies of healthy women using ECPs and reported AEs—Thirty-five studies (3 UPA studies, 1 UPA and LNG study, 10 LNGs studies, 18 Yuzpe studies and 3 LNG and Yuzpe studies) examined AEs among populations of healthy women taking ECPs. Of these, 32 articles examined ECP use among healthy women with sample sizes ranging from 32 to 4129 women and reported no serious AEs [18,21,23–52]. Three studies reported AEs other than common ECP side effects (e.g., nausea, vomiting, changes to bleeding patterns) [14,20,22]. In the first of these studies, which randomized 2221 healthy women to

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UPA or LNG for EC, there were two serious AEs considered potentially related to EC use: one case of dizziness in the UPA group and one case of molar pregnancy in the LNG group [20]. The second of these studies was a report of postmarketing pharmacovigilance that included 553 women who reported adverse drug reactions (ADRs) after taking UPA [14]. Eight serious AEs were reported, but only one episode of fainting was considered related to UPA intake. There was not enough information to determine causality for a stroke, which occurred 4 months after intake, an acute allergy reaction, a seizure in an epileptic patient or a ruptured ovarian cyst. The remaining serious AEs were not considered related to UPA use. Finally, an analysis of the General Practice Research Database included 73,302 women <50 years old who received over 100,000 prescriptions for EC. This analysis identified 19 first-time diagnoses of venous thromboembolic events (VTE) [22]. Cases had no other risk factors for VTE, and all received anticoagulation therapy. In this study, current exposure to ECPs was defined as a prescription within 45 days before the date of first diagnosis of VTE (the index date). Of the cases identified, no cases were categorized as current exposure to ECPs [crude incidence rate for ECP exposure 0/100,000 person–years, 95% confidence interval (CI): 0–30.9 for current ECP users] compared with an incidence rate of 3.0/100,000 person-years (95% CI: 1.4–6.6) for women categorized as no exposure to ECPs, COCs or pregnancy.

3.2.3. Studies of healthy women with reported pregnancy outcomes after ECP exposure—We identified nine trials or observational studies and one pharmacovigilance study that examined ECP efficacy among healthy women and reported pregnancy outcomes for EC failures (Table 2) [12–20]. In the seven studies that examined efficacy of ECP regimens and reported pregnancy outcomes after EC failures, 76 pregnancies were reported in two LNG studies (one ectopic pregnancy and 64 terminations in one study and four pregnancies continued to deliver live, healthy infants and remaining 7 lost to follow-up) [12,18]; 72 pregnancies were reported in 3 Yuzpe studies [no ectopics and 11 continued (not terminated) pregnancies, with normal births or healthy infants reported [13,15,17] and one study reported “some” spontaneous abortions with no further details]; 42 intrauterine pregnancies were reported in one randomized controlled trial (RCT) comparing Yuzpe to LNG (five continued with reported normal outcomes and the remainder of pregnancies were terminated) [16]; 50 pregnancies were reported in an RCT comparing UPA to LNG (almost all were terminated except five spontaneous abortions after LNG, including a molar pregnancy, four spontaneous abortions after UPA, three term deliveries after LNG with no further details and four women were lost to follow-up) [20]. Seven pregnancies were observed in the one study that did not examine efficacy but compared probabilities of pregnancy using LMP with ultrasound findings among women using either Yuzpe or LNG; three pregnancies were carried to term with no further details given, and four were voluntarily terminated [19]. The one remaining study reported postmarketing pharmacovigilance data from the manufacturer of UPA [14]. Of an estimated 1.4 million women from 23 countries who had taken UPA by the time of this analysis, 282 pregnancies had been reported with 30-mg dose of UPA. Follow-up outcomes were available for 132 of these pregnancies, including 4 ectopic pregnancies, 17 spontaneous abortions, 20 live births with normal infants and 93 elective terminations. One case of trisomy 21 was reported in a 42 year-old woman, but this was not considered related to UPA, due to timing of exposure.

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One case of fetal cardiac defect was also reported, and relationship to drug exposure was assessed as uncertain. Among 94 pregnancies at doses varying between 10 mg and 200 mg, which differ from the usual 30-mg dose used for EC, 11 pregnancies were lost to follow-up, and 8 births with 9 healthy infants were reported. There were no ectopic pregnancies, 17 spontaneous abortions and 58 elective terminations reported.

4. Discussion

Direct evidence examining adverse outcomes with the use of UPA, LNG or Yuzpe ECPs among women with certain characteristics or medical conditions is limited to five studies: one study examining LNG use among pregnant women (Level II-2, quality fair), one study examining either LNG or Yuzpe use among pregnant women (Level II-2, quality poor), two studies examining LNG use among BF women (Level I, II-2, quality poor, fair) and one study examining repeated ECP use and the risk of ectopic pregnancy (Level II-2, quality fair). No articles reported direct evidence for other conditions in the WHO or US MEC for LNG or Yuzpe use, and no articles were identified that examined the safety of UPA use among women with any specific medical conditions or personal characteristics included in the WHO or US MEC.

The two cohort studies, one retrospective and one prospective, examining LNG or Yuzpe use among pregnant women were fair to poor quality and found no serious AEs among women or infants and no increased risk of congenital malformations with ECP use [9,10]. While both studies assessed confounders and groups appeared similar at baseline, they were limited by small sample sizes, especially considering the rare outcome of congenital malformations, and neither provided a priori power calculations to assess the ability to detect differences between groups. One of the studies recruited subjects from a teratology information service and compared those exposed to LNG to those calling about other nonteratogenic drugs. Women accessing teratology information service hotlines may not be generalizable to the general population of pregnant women. The other study, however, recruited exposed and unexposed women prospectively from the first prenatal visit at outpatient clinics. Overall, there were no differences in malformations or birth defects between exposed and unexposed groups in either study.

Two studies among BF women found no AEs with LNG ECP use among women or infants, and minimal or no adverse effects on BF were reported compared with groups unexposed to LNG ECPs. The two BF studies included a prospective study of poor quality that was designed to look at subjective BF outcomes and a fair quality RCT that randomized women to standard postpartum contraception counseling with or without EC counseling and advance provision to assess rates of initiation of regular contraception [7,8]. Overall, measures of BF performance were poorly described and self-reported. The prospective study limited participants to BF women selected from a teratology information service who had follow-up data available. The study sample was selected entirely from women using this service, creating a large potential for selection bias, as women having problems may be more likely to call. The unexposed group was also using progestin-only contraception but at lower doses and on a regular basis. Other limitations included the small sample size, and the lack of a power calculation to determine sample sizes needed to detect differences between those

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exposed and those unexposed to LNG ECPs. The RCT included a large sample size, similarity between groups at baseline and complete follow-up. This study, however, did not discuss randomization allocation, did not report any infant outcomes and used self-report for BF outcomes. The one PK study examined venous and milk samples from BF mothers after taking 1.5-mg LNG and found that, while LNG can be found in breast milk following ECP use, maximum infant exposure was estimated to be 1.6 mcg over 24 h. The one matched case–control study that compared repeated use of LNG ECPs with nonuse among women with ectopic pregnancies and intrauterine pregnancies found no increased odds of ectopic pregnancy [4]. This (fair quality) study included a large sample of Chinese women, matched by age, marital status and gestational age, and clearly described identification of cases and controls and adjusted for several potential confounders. The study, however, was limited by the self-reported nature for the exposure of interest, use of LNG ECPs.

Of thirty-five indirect studies that reported AEs among healthy women taking ECPs, only three studies reported serious AEs, including an episode of fainting, an episode of dizziness and a molar pregnancy [14,20]. There was no increased risk of VTE among EC users in an analysis of the General Practice Research Database [22].

We also identified indirect evidence that examined ECP use among healthy women for whom pregnancy outcomes or AEs were reported, including 7 effectiveness trials, one case series and one pharmacovigilance report that reported pregnancy outcomes among healthy women taking UPA, LNG or Yuzpe as indirect evidence [12–20]. No compar-isons were made for pregnancy outcomes between different formulations of ECPs or for women not exposed to ECPs. While most pregnancies were terminated, few spontaneous abortions occurred with rates similar to the general population, ectopic pregnancies were rare and normal or healthy outcomes were reported for all pregnancies that were continued and followed to delivery.

While these studies do not directly answer whether women with certain medical conditions or characteristics can safely take ECPs, the cumulative evidence for thousands of women taking UPA, LNG or combined estrogen–progestogen ECPs suggests that AEs among healthy women are rare.

5. Conclusion

Only five studies directly addressed our study question and examined LNG and Yuzpe use among pregnant or BF women or women with repeated use of LNG ECPs (Level I, II-2, poor to fair), while the other studies included in this review provided only indirect evidence reporting pregnancy outcomes or AEs among healthy women taking UPA, LNG or Yuzpe. However, both direct and indirect evidence for our study question did not suggest any special safety concerns for the use of ECPs among women with particular medical conditions or personal characteristics.

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Appendix A

("Contraception, Postcoital"[Mesh] OR "Contraceptives, Postcoital"[MeSH] OR emergency contracept* OR "morning after pill" OR postcoital contracept* OR yuzpe AND ("Contraceptives, Oral, Combined"[Mesh] OR "Contraceptives, Oral"[Mesh] OR "combined oral contraceptives" OR "oral contraceptives" OR "levonorgestrel"[Mesh] OR levonorgestrel OR LNG AND (emergency OR "morning after" OR postcoital)) OR plan b OR ulipristal OR UPA OR CDB-2914) AND ("Pregnancy"[mesh] OR pregnan* OR "pregnancy complications"[mesh] OR "Breast Feeding"[Mesh] OR breastfe* OR breast fe* OR "Pregnancy, Ectopic"[Mesh] OR ectopic pregnanc* OR ovarian pregnanc* OR "Cardiovascular Diseases"[Mesh] OR cardiovascular OR ischem* OR ischaem* OR thromboe* OR thrombosis OR thrombotic OR "Cerebrovascular disorders"[mesh] OR (cerebrovascular AND (disorder OR attack)) OR "Angina Pectoris"[Mesh] OR angina OR "Migraine Disorders"[Mesh] OR migraine* OR "Liver Diseases"[Mesh] OR liver disease* OR hepatitis OR cirrhosis OR hepatocellular OR jaundice OR repeat* OR "Rape"[Mesh] OR "Incest"[Mesh] OR "sex offenses"[mesh] OR rape* OR incest* OR "sexual trauma" OR "sexual violence" OR "sexual abuse").

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Table 1

Direct evidence for adverse outcomes with use of LNG, UPA and Yuzpe ECPs among women with certain medical conditions or characteristics.

Author, year, county, funding source	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs	Strengths	Weaknesses	Quality
LNG								
Pregnant women								
Zhang L, 2009, China [10] China National Science and Technology Ministry, Shanghai Population and Family Planning commission grants	Prospective cohort	332 pregnant women exposed to LNG EC in conception cycle (0.75 mg-9 mg), 272 infants 332 pregnant women without LNG exposure recruited from outpatients, matched for DOB and LMP, 298 babies	LNG (dosage range: .75–9 mg; 84.4% took 1.5 mg)	Congenital malformations, perinatal complications and delivery circumstances	First trimester miscarriage: LNG+: 31 (10.3%), 4 malformations LNG−: 28 (8.6%, p=0.47), 4 malformations (not significant) Second trimester terminations due to fetal malformation:LNG+: congenital polycystic kidney LNG−: sacrococcygeal tumor, Achondroplasia No differences in fetal development at 1st or 2nd ultrasound. No differences in rates of birth defects LNG+:1.5% LNG−: 1.3% (RR 1.10, 95% CI, 0.28, 4.37) 3 newborn malformations in LNG+ group: hip dislocation, small incomplete cleft lip and facial hemangioma 2 newborn malformations in LNG group: cleidocranial dysplasia and girl with anus fistula No difference in rate of pathologic pregnancy outcome between groups (previa, abruption, velamentous cord, GDM, PIH, ICP, PROM, oligohydramnios, fetal distress, dystocia or total pregnancy complications) One IUFD, one PTL at 35 weeks with TTN in study group In comparison group, one CS	No other teratogenic exposure within 3 months for either group; other potential confounders assessed and found similar between groups Exposure and outcome ascertainment well defined Examined dosages of LNG used Low attrition in both groups (< 2%)	No power calculation Small sample size for rare events No infant follow-up after delivery	II-2, fair

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Author, year, county, funding source	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs	Strengths	Weaknesses	Quality
					at 37 weeks with resolutive tachypnea			
De Santis, 2005, Italy [9] Source of funding not reported	Retrospective cohort	Exposed: Pregnant women contacting teratology information service after EC failure in first trimester (*n*=36) Unexposed: Pregnant women calling about nonteratogenic drugs (*n*=80) *n*=10 cases exposed to other drugs *n*=2 cases exposed to other known teratogenic drugs (valproic acid and phenobarbitone in 1 epileptic patient, and methimazole treatment in 1 hyperthyroid patient). *N*=25 exposed neonates *N*=60 nonexposed neonates	Exposure: LNG: *n*=25 or Yuzpe (EE +LNG): *n*=11	Rate of congenital anomalies, abortion rate, ectopic pregnancies, gestational age at birth, birth weight and length, prepartum or peripartum complications.	Prenatal exposure among cases range 10 days to 45 days of pregnancy (unknown if by LMP or date of conception) Pregnancy outcomes: No increased risk of (p reported as not statistically significant): Spontaneous abortion: EC+: 6/36, 17% EC−: 3/80, 4% Stillbirth: EC+: 0/36, 0% EC−: 1/80, 1% No ectopic pregnancies in either group No maternal complications in either group Neonatal outcomes (*n*=25 exposed neonates): Congenital anomalies EC+: 1 (Rubella-related malformation) EC−: 1 (planus hemangioma on the arm) Neonatal complications: EC+: 2 (1 case of gastroesophageal reflux requiring medical treatment, 1 case of nasolacrimal duct obstruction, surgically drained) EC−: 0 No increased risk malformations No difference in length or weight No congenital abnormalities observed in 2 infants exposed to ECP + other teratogen.	Assessed potential confounders, including other medications used Timing by day of exposure collected	LNG and Yuzpe examined together Small sample size No power calculation Unclear if outcomes ascertained by patient report or medical record	II-2, poor
BF women								
Polakow-Farkash, 2013, Israel [7] Source of funding not reported	Prospective cohort	Exposed: BF women contacting teratology information service who used EC (*n*=71 mothers, and *n*=72 infants) Unexposed: BF women calling about ethynodiol diacetate or	LNG (dose not specified)	Effects of LNG during BF on infants, mothers or milk volume	No reported adverse effects of LNG during lactation on feeding or behavior of infant Transient irritability in 2 control infants; one control infant diagnosed with	Only included those with follow-up Women informed to take LNG after BF and resume	No power calculation for primary outcome Wide range of follow-up questionnaire between 6	II-2, poor

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Author, year, county, funding source	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs	Strengths	Weaknesses	Quality
		desogestrel and breastfed infants (*n*=72) Questionnaires administered at 6 months and 12 years			hypertrichosis *n*=1 infant in LNG group had weight < 5th percentile at 1 year *n*=1 infant in control group had slow development at 1 year No difference in subjective estimation of milk volume (7% vs. 6%, p=0.74) 75% BF women discontinued for less than 8h after LNG 2/71 women in LNG group did not reinitiate BF. Side effects in LNG group mothers:Vaginal bleeding: *n*=11 Dizziness: *n*=1	BF Assessed potential confounders and similar between groups (infants significantly older among study group at initial encounter and at follow-up)	months to 2 years after initial consultation Outcomes by self-report and potential for recall bias with long follow-up time Potential for selection bias, as women experiencing problems may have been more likely to call in. Comparison group was also exposed to progestin-only contraception (lower dose and different progestins, but on a regular basis)	
Shaaban, 2013, Egypt [8] Mini-grant from Department of Public Health, Assiut University and Johns Hopkins Bloomberg School of Public Health joint project	Open-label RCT	Women intending to use LAM for 6 months and breastfeed for 1 year after singleton live birth were randomly assigned to: LAM-only group or LAM + EC counseling + advance provision of one packet of EC group (*n*=579 per arm) to use with loss of LAM prerequisites All received postpartum contraceptive counseling Excluded women planning to use other method of contraception shortly after delivery and those taking medications for chronic diseases. Followed to 6 months postpartum.	0.75-mg LNG q12h × 2 doses	Start of regular contraception, use of EC, side effects, pregnancy	No difference in duration of lactation, resumption of menstruation or pattern of BF 44.2% women in EC arm used ECPs Of these, 30% complained of nausea, 2.9% complained of vomiting. Mothers who used EC did not report changes over time in quantity of milk or infant health.	Large sample size Potential confounders assessed and groups appear similar at baseline 100% follow-up at 6 months	Randomization allocation not described Not designed to detect differences in BF outcomes by LNG exposure Infant outcomes not reported	I, fair
Repeated ECP use								
Zhang, 2015, China [4] Shanghai Scientific and	Matched case-control	Cases: Women with ectopic pregnancy according to ACOG diagnostic criteria identified in the inpatient department of gynecology	LNG use within the last year (single or double doses) Nonuse	Ectopic pregnancy IUP	Adjusted OR (95% CI) for ectopic pregnancy vs. IUP: Not used: Reference 1–2 times: 1.17 (0.99–1.38)	Matched analysis Large sample size Case and control	Identification of risk factors including LNG ECP use by self-report	II-2, fair

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Author, year, county, funding source	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs	Strengths	Weaknesses	Quality
Technical Committee Grants		(*n*=2411) Controls: Women with intrauterine pregnancies matched 1:1 by age +/− 5 years, marital status and gestational age identified from prenatal clinic and family planning clinic (*n*=2419)			3–4 times: 0.93 (0.74–1.17) ≥ 5 times: 0.85 (0.66–1.11) p for trend 0.67	identification described Several adjustments made for potential confounders		

q12h: every 12 h; GDM: gestational diabetes mellitus; PIH: pregnancy-induced hypertension; ICP: intrahepatic cholestasis of pregnancy; PROM: premature rupture of membranes; IUFD: intrauterine fetal demise; PTL: preterm labor; TTN: transient tachypnea of the newborn; CS: caesarean section; ACOG: American College of Obstetricians and Gynecologists.

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Table 2

Indirect evidence for adverse outcomes with use of LNG, UPA and Yuzpe ECPs among women with certain medical conditions or characteristics or among healthy women.

Author, year, country	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs
BF women					
LNG					
Gainer, 2007, Chile [11] HRA Pharma	PK study, 120 h	Healthy, nonsmoking, exclusively BF women between 6 and 12 weeks postpartum, in lactational amenorrhea, not on hormonal contraceptives or other hormones with healthy infants (n=12) Pretreatment phase: pump milk until adequate amount conserved for 72 hour period after LNG dosing Treatment phase: 1.5-mg LNG and sample collection of blood and milk Post treatment phase: follow-up collection within 72h of LNG Exclusion criteria: Irregular menstrual cycles before pregnancy, inadequate baby weight (n=2), moderate hypercholesterolemia (n=1), excess weight (n=1), menstruation (n=1).	1.5-mg LNG × 1 dose	PKs of LNG EC in healthy BF female volunteers: venous samples before and 1, 2, 4, 6, 8, 24, 48, 72, 96 and 120h after LNG administration for LNG and SHBG assays; milk samples manually expressed before and at 2, 4, 6, 8, 24, 48, 72, 96 and 120h after LNG immediately after blood samples taken Infant sampling not performed (infants not exposed); exposures to infants estimated from LNG AUC in milk (24 h).	AEs: No serious AEs related to study treatment reported. woman diagnosed with choledocolithiasis as a result of a clinical condition that arose posttreatment. 4 women and 6 infants experienced AEs; none assumed to be drug-related. AEs not listed. PK parameters of LNG in plasma: T_{max}: 2 h C_{max}: 15.4 ng × ml^{-1} AUC_{0-t}: 252.8 ng × h × ml^{-1} $AUC_{0-\infty}$: 262.6 ng × h × ml^{-1} $T_{1/2\ (h)}$:29.3 h PK parameters of LNG in breast milk: T_{max}: 3.9 h C_{max}: 7.0 ng × ml^{-1} AUC_{0-t}: 65.3 ng × h × ml^{-1} $AUC_{0-\infty}$: 67.0ng × h × ml^{-1} $T_{1/2\ (h)}$: 26.3 h Estimated infant exposure after 1.5-mg LNG dose: 0–24 h: 1.6 mcg (0–8 h: 1.0 mcg; 8–24 h: .6 mcg) 24–48 h: .3 mcg 48–72 h: .2 mcg
EC failures					
LNG					
Arowojolu, 2002, Nigeria [12] Source of funding not reported	Double-blind RCT, 1 cycle	Healthy noncontracepting women reporting for EC ≤ 72 h after unprotected sex at a university hospital or Planned Parenthood clinic, with regular menstrual cycles (21–35 days), had intercourse within ovulation period, gave written informed consent. Exclusion criteria: not available for follow-up, pregnant, contraindications to hormonal contraception. Group A: took 1.75-mg LNG tablet + 1 placebo and repeated 12 h later (n=518 analyzed)	0.75-mg LNG × 2, repeated after 12 h 1 dose of 1.5-mg LNG	Efficacy and safety of LNG ECPs taken as . 0.75-mg LNG q12h × 2 doses vs. 1 dose of 1.5-mg LNG	11 intrauterine pregnancies. No ectopic pregnancies 3 women continued pregnancies and delivered live, healthy infants (others lost to follow up).

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Author, year, country	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs
		Group B: took 2 .75 mg LNG tablets (1.5-mg LNG total) + 2 placebos 12 h later (*n*=544 analyzed)			
Von Hertzen, 2002, China, Finland, Georgia, Hungary, India, Mongolia, Slovenia, Sweden, Switzerland, UK [18] UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction, WHO; LNG and placebo tablets provided by Gedeon Richter, Budapest, Hungary; Mifepristone and placebo tablets provided by Roussel-Uclaf, Romainville, France	Double-blind RCT, 10 countries, 6 weeks	Healthy women presenting for EC ≤ 120 h after single act of unprotected sex, with regular menstrual cycles (24–42 days), willing to abstain from unprotected sex in current menstrual cycle, available for follow up at 6 weeks. Exclusion criteria: Pregnant, BF, recent pregnancy or hormonal contraceptive use without resumption of regular menstrual cycle, use of hormonal contraception in current cycle, use of rhythm method. Women randomized to receive: single dose of 1.5-mg LNG (*n*=1379, *n*= 1359 included in safety analysis) Two doses of .75 mg LNG taken 12 h apart (*n*= 1377, *n*= 1361 included in safety analysis) Single dose of 10 mg mifepristone (*n*= 1380)	1.5-mg LNG (single dose or 2 separate doses of .75 mg LNG taken 12 h apart)	Efficacy and side effects of three treatments administered ≤ 120 h after unprotected intercourse: single dose of 10 mg mifepristone vs. single dose of 1.5-mg LNG vs. 2 separate doses of .75 mg LNG taken 12 h apart	65 pregnancies: −1 ectopic pregnancy requiring surgical treatment (2 dose LNG group) - all other pregnancies terminated
Yuzpe					
Ellertson, 2003, US and UK [13] Grants from the William and Flora Hewlett Foundation, David & Lucile Packard Foundation, Open Society Institute, May Wohlford, John Snyder, the Population Council, an anonymous donor, and Irving and Roberta Schneiderman	Double-masked, multi-center RCT, 6 months	Women presenting at 5 clinic sites in US and UK, aged 16–45, with regular cycles (21–35 days), presenting within 3 days of unprotected sexual intercourse that occurred 10 to +6 days from estimated day of ovulation, willing to abstain from further unprotected intercourse in cycle, attend follow up visit and keep diary of side effects, refused Cu IUD or LNG-alone for EC. Exclusion criteria: Pregnant, BF, use of hormonal contraception in past 2 months, abnormal periods in previous 2 cycles. Standard Yuzpe: *n*=675 (typical use) EE + norethindrone: *n*=650 (typical use) Single dose Yuzpe: *n*=648 (typical use)	3 Yuzpe groups: 1) Standard Yuzpe (EE+LNG) 2) 1 mg EE + 2-mg norethindrone 3) Single dose Yuzpe regimen (100-mcg EE + 1 mg LNG), followed by placebo taken 12 h later.	Effectiveness of norethindrone in Yuzpe. Effectiveness of Yuzpe when second dose is removed. Side effects and treatment regimens' acceptability. Whether treatment works better if started sooner, and whether taking with food reduces nausea and vomiting.	58 pregnancies observed, all intrauterine. 8 pregnancies for which data were available resulted in normal births. Some pregnancies ended in spontaneous abortion; number not reported.
Severi, 2002, Italy [19] No source of funding reported	Case series	Women seeking EC within 36 h of single act of unprotected intercourse (*n*= 163)	Yuzpe: 100-mcg EE + 500-mcg LNG q12h × 2 doses) LNG: 0.75-mg q12h × 2 doses	Probability of conception using ultrasound finding versus day of LMP	7 pregnancies: −3 carried successfully to term −4 voluntary terminations
Webb, 1992, UK [15] Special programme of research, development and research training in human reproduction ofthe WHO	RCT, 1 cycle	Women requesting EC ≤ 72 h after single act of unprotected intercourse, with regular cycles (21–35 days; no individual variation > 4 days over previous 3 months), aged 16–45, willing to consent, available for follow up. Exclusion criteria: Pregnancy within previous 3 months, contraindications to estrogen/progestin (thromboembolic disease, liver disease, breast cancer, diabetes, jaundice, or pruritus of pregnancy), known of Yuzpe: *n*=191 women randomized suspected adrenal disease, taking interactive drugs (liver enzyme inducers, broad spectrum antibiotics), use of sex steroids since last menstruation.	Yuzpe (100-mcg EE + 500-mcg LNG q12h × 2 doses	Effectiveness and side effects of Yuzpe vs. Danazol vs. mifepristone for EC.	5 women in Yuzpe group became pregnant: had vaginal deliveries of normal female infants voluntary terminations 1 woman already pregnant when given Yuzpe had voluntary termination

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Author, year, country	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs
Zuliani, 1990, Italy [17] Source of funding not reported	RCT, 4 weeks	Women presenting at family planning center in Milan requesting EC ≤ 72 h after unprotected intercourse given either Yuzpe of Danazol for EC. Of Yuzpe group, 78.8% aged 15–25, 84.2% nulligravidae. Exclusion criteria: Contraindications to steroids, irregular cycles (<21 or > 35 days), > 1 instance of unprotected intercourse in month, postpartum/ postabortion amenorrheic women, patients who had forgotten only 1 OCP. Yuzpe group: *n*=407 received EE-NG	Yuzpe: 0.05-mg EE/ 0.5-mg norgestrel, 2 tablets, q12h × 2 doses Danazol	Efficacy and side effects of two Danazol regimens vs. Yuzpe for EC.	9 pregnancies reported after failure of Yuzpe (*n*=8 voluntarily terminated; *n*=1 delivered at term by Cesarean section; healthy female weighing 300g).
LNG/Yuzpe					
WHO Task Force on Postovulatory Methods of Fertility Regulation, 1998, Australia, Canada, China, Georgia, Hungary, India, Mongolia, New Zealand, Nigeria, Panama, Slovenia, Sweden, United Kingdom, United States [16] UNDP/ UNFPA/WHO/World Bank Special Programme of Research, Development, and Research Training in Human Reproduction, WHO; Drugs and packaging provided by Gedeon Richter, Budapest, Hungary	Double-blind RCT, 21 centers in 14 countries, 1 cycle	Healthy women with regular menstrual cycles (24–42 days) who had one act of unprotected intercourse ≤ 72 h before treatment. Participants asked to avoid further unprotected sex during treatment cycle. Mean age: 27 years. Previous hormonal contraception users included only if ≥ 1 normal cycle before current cycle. Exclusion criteria: BF, use of hormonal contraception in current cycle, contraindications to hormonal contraception, uncertainly about date of LMP. Yuzpe: *n*=997 enrolled LNG: *n*= 1001 enrolled	Yuzpe (.05 mg EE + .25 mg LNG × 2, repeated after 12 h) LNG (.75 mg) + placebo × 2, repeated after 12 h	Efficacy and side effects of Yuzpe vs. LNG for EC	Of 42 total pregnancies (*n*=4 pregnant at baseline), all intrauterine. 5 pregnancies continued with normal outcomes; other pregnancies terminated.
LNG/UPA					
Glasier, 2010, UK, Ireland, US [20] HRA Pharma	Multicenter RCT, followed until return of menses or 60 days after treatment, and meta-analysis (to examine efficacy)	Women with regular menstrual cycles (24–35 days) seeking EC within 120 h of unprotected sex, aged > 16 years old (> 18 years old in US). Exclusion criteria: Pregnant, BF, sterilized. Women randomized to UPA (*n*= 1104) or LNG (*n*= 1117). Women presenting 72–120 h after unprotected sex initially offered Cu IUD. Women requesting EC in subsequent cycles could reenroll.	30-mg UPA 1.5-mg LNG	Efficacy and safety of UPA vs. LNG taken ≤ 120h after unprotected sex	UPA: *n*=20 pregnancies LNG: *n*= 30 pregnancies 34/50 pregnancies terminated (UPA: *n*= 14, LNG: *n*=20) Spontaneous abortion *n*=9 (UPA: *n*=4, LNG: *n*=5, including 1 molar pregnancy). Continued to term *n*=4 (UPA: *n*=1, lost to follow-up; LNG: *n*=3, delivered at term).lost to follow up: *n*=3 (UPA: *n*=1, LNG: *n*=2)
UPA					
Levy, 2014, 23 countries (not listed) [14] HRA Pharma	Postmarketing pharmacovigilance data collection	Estimate over 1,400,000 women exposed to UPA for EC from internal sales data 553 women reported *n*= 1049 ADRs from 23 countries	UPA	ADRs from spontaneous health care professional reports or through manufacturer's pregnancy registry online	Pregnancy outcomes (30 mg): Total pregnancies reported: *n*=282 Loss to follow up: *n*= 133 Ongoing: *n*=15 Ectopic: *n*=4 Spontaneous miscarriage: *n*=17

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Author, year, country	Study design	Population, intervention	Type(s) of EC	Primary and secondary outcomes	AEs
					Elective termination: *n*=93 Live birth: *n*=20 Pregnancy outcomes (10–200 mg): Total pregnancies reported: *n*=94 Loss to follow up: *n*=11 Ongoing: *n*=0 Ectopic: *n*=0 Spontaneous miscarriage: *n*=17 Elective termination: *n*=58 Live birth: *n*= 8 births, 9 babies (twins)

C_{max}: peak serum concentration that a drug reaches after administration; T_{max}: time to C_{max}; AUC: area under the curve; $t_{1/2}$: biological half-life of drug; EE: ethinyl estradiol; Cu IUD: copper intrauterine device; EE-NG: ethinyl estradiol + norgestrel.