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Ulipristal versus Levonorgestrel for Emergency Contraception: A Review of Comparative Clinical Effectiveness and Guidelines

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Abbreviations

BMI	body mass index
ECP	emergency contraceptive pill
IUD	intrauterine device
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
SR	systematic review
WHO	World Health Organization

Context and Policy Issues

Emergency contraception refers to methods of contraception used in order to prevent pregnancy after sexual intercourse and include copper-bearing intrauterine devices (IUDs) and emergency contraceptive pills (ECPs).[1] Contrary to regular forms of contraception, emergency contraception is intended for occasional use when contraceptive failure or unprotected intercourse has occurred.[2] Oral pills are easier to access and administer than intrauterine devices.[3] The oral pills that the World Health Organization (WHO) recommends for emergency contraception are levonorgestrel, ulipristal acetate (to be referred to as "ulipristal" for the duration of this report), and combined oral contraceptive pills that contain estradiol and levonorgestrel.[1] Levonorgestrel is approved by Health Canada for the prevention of pregnancy and is intended to be used within 72 hours or three days after known or suspected contraceptive failure or unprotected intercourse.[4] Ulipristal is approved for the prevention of pregnancy when taken within 120 hours or five days of unprotected intercourse or a known or suspected contraceptive failure.[5]

When used within five days, the rates of pregnancy associated with levonorgestrel and ulipristal have been found to be 2.2% and 1.3%.[3] However, there are several factors that may modify the effectiveness of these two drugs including body mass and the time within the fertile window in which intercourse occurred.[3,6] Both levonorgestrel and ulipristal have been found to be safe and associated with occasional mild side effects.[1] The side effects include nausea and vomiting, slight irregular vaginal bleeding, and fatigue.[1]

Access to emergency contraception in Canada

In Canada, the access to levonorgestrel and ulipristal are not the same. A prescription is required for ulipristal and levonorgestrel can be purchased either over or behind the counter.[7,8]

In 2014, Health Canada issued a warning that levonorgestrel might not be as effective for individuals weighing more than 165 pounds.[2,8] The role of the factors modifying the effectiveness of emergency contraception are important. This review aims to compare the effectiveness of levonorgestrel and ulipristal for emergency contraception based on the latest evidence.

Research Questions

1. What is the comparative clinical effectiveness of ulipristal versus levonorgestrel for use as emergency contraception?
2. What are the evidence-based guidelines regarding the use of ulipristal?

Key Findings

For the comparative clinical effectiveness of ulipristal versus levonorgestrel for use as emergency contraception, two randomized controlled trials (RCTs), were synthesized in one moderate-quality and one critically low-quality systematic reviews. One evidence-based guideline for Canadian practitioners by the Society of Obstetricians and Gynaecologists of Canada was identified. There is evidence to show that ulipristal is more effective than levonorgestrel to reduce the risk of pregnancy five days after unprotected intercourse. The included meta-analysis found that there was no evidence to show differences in the risks of adverse effects, including nausea and vomiting between the two agents. One SR concluded that a BMI greater than or equal to 30 was associated with an increased risk of pregnancy after using levonorgestrel but not ulipristal for emergency contraception. This corresponded to the guideline that indicated ulipristal is recommended for those with a BMI equal to or greater than 25 who are seeking emergency contraception. Due to limited evidence and heterogeneity in the doses, further research addressing ulipristal versus levonorgestrel may help to reduce uncertainty.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD), Medline, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01, 2013 and September 28, 2018.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Those requesting emergency contraception - Subgroups of interest: BMI >25; BMI >30
Intervention	Ulipristal acetate
Comparator	Levonorgestrel
Outcomes	Q1 – Clinical effectiveness (i.e. effectiveness in preventing pregnancy); safety/adverse events Q2 – guidelines and recommendations for use
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

BMI = body mass index

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2013. Studies included in a selected systematic review were also excluded. If multiple systematic reviews had a full overlap of included studies but did not report unique outcomes, the most comprehensive was selected.

Critical Appraisal of Individual Studies

Systematic reviews (SRs) were critically appraised with the AMSTAR II checklist.[9] Guidelines were assessed with the AGREE II instrument.[10] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations assessed in each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 393 citations were identified in the literature search. Following screening of titles and abstracts, 368 citations were excluded and 25 potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search for full text review. Of these potentially relevant articles, 23 publications were excluded for various reasons, and three publications met the inclusion criteria and were included in this report. These comprised two systematic reviews and one evidence-based guideline. Although the two systematic reviews had full overlap in the included studies relevant to this review, both were selected as they reported different outcomes. Appendix 1 presents the PRISMA[11] flowchart of the study selection. Additional references of potential interest are provided in Appendix 6.

Summary of Study Characteristics

Additional details describing the characteristics of the included studies are reported in Appendix 2.

Study Design

The two systematic reviews (SRs) were published in 2017 and 2016.[2,12] One evidence-based guideline was published in 2015.[7] Two primary studies, Creinin 2006 and Glasier 2010, were included in the two SRs.[2,12] The overlap between the included SRs is tabulated in Appendix 5.

The evidence-based guideline was prepared by the Contraception Consensus Working Group and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada.[7] The search for the literature to support the recommendations was mentioned, but the guideline development process was not described.[7] Quality of evidence was based on the Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.[7]

Country of Origin

The first authors of the SRs by Shen et al. and Jatlaoui et al. were based in China and the USA respectively.[2,12] The guideline authored by Black et al. was applicable to health care providers in Canada.[7]

Patient Population

In the two RCTs included in the SRs, those receiving emergency contraception with known pregnancy status were included.[2,12]

The guideline by Black et al. provided recommendations for contraception practice in Canada.[7] In Chapter 3, the recommendations were specific to populations using emergency contraception.[7]

Interventions and Comparators

In the SR by Shen et al., emergency contraception methods were compared, including an IUD and hormonal treatment.[2] Jatlaoui et al. compared hormonal interventions by BMI status.[12] In the two RCTs included in the SRs, Creinin 2006 and Glasier 2010, ulipristal was the intervention and levonorgestrel was the comparator.[2,12] The dosage of ulipristal in one primary study (Creinin 2006) was a single oral 50 mg dose within 72 hours of unprotected intercourse, and the dosage in the other primary study (Glasier 2010) was a single oral 30 mg dose within 120 hours of unprotected intercourse.[2] Both doses of ulipristal were considered bioequivalent by European Medicines Agency (EMA) and the Food and Drug Administration (FDA, USA).[2]

The dosage of levonorgestrel in one primary study (Creinin 2006) was two oral doses of 0.75 mg (12 hours apart), and in the other primary study (Glasier 2010), a single oral dose of 1.5 mg.[2]

In the guideline by Black et al., copper IUDs (that were not of interest for this review) and hormonal treatment, including ulipristal and levonorgestrel were evaluated and recommendations for clinical practice were made accordingly.[7]

Outcomes

Pregnancy rates were the outcome reviewed in the SRs by Shen et al. and Jatlaoui et al.[2,12] Jatlaoui et al. aimed to determine the difference in pregnancy rates based on body mass index (BMI).[12] The other outcomes of interest in the SR by Shen et al. were side effects and menses.[2]

Summary of Critical Appraisal

Additional details describing the critical appraisal of the included studies are reported in Appendix 3.

Systematic reviews

In the two SRs by Shen et al. and Jatlaoui et al., the population, intervention, comparator, and outcome (PICO) criteria were specified.[2,12] A comprehensive literature search was conducted and the included studies were described in detail in the two SRs.[2,12] Quality assessment tools were used to critically appraise the primary studies.[2,12] Risk of bias was considered while drawing the conclusions.[2,12]

The protocol of the Cochrane SR by Shen et al. was published *a priori*.[2] Shen et al. explained the study selection criteria, selected the studies in duplicate, extracted the data in duplicate, provided a list of excluded studies, adopted appropriate statistical methods to meta-analyze, investigated publication bias for meta-analyses with ten or more primary studies, and declared review authors' conflict of interest.[2] The risk of bias due to incomplete

literature search, inappropriate statistical synthesis and researchers' preference to certain studies could be minimized.

In contrast, protocol publication, study selection criteria, independent study selection, details in excluded studies, and publication bias assessment were not mentioned in the other SR.[12] Jatlaoui et al. reported the funding sources of the primary studies and declared review authors' conflict of interest.[12]

Evidence-based guidelines

The overall objectives, health questions, populations to whom it was meant to apply, and target users of the guideline for contraception practice in Canada were described.[7] A comprehensive literature search was mentioned.[7] The supporting evidence was listed along with the recommendations.[7] The recommendations were specific, unambiguous and easy to identify.[7] For certain situations, options for management of the conditions were provided.[7] The facilitators and barriers to its application and the advices on guideline implementation were described.[7]

However, the recommendation development process was not well elaborated.[7] The selection of the guideline development group, patient or public engagement, evidence selection criteria, methods to formulate the recommendations, external review, update procedures, potential resource implications, auditing criteria, and conflict of interest were not described.[7] Without a systematic approach to select and synthesize the evidence, the guideline might be subject to issues, such as lack of stakeholder involvement, scientific rigour of evidence integration, limited applicability, and conflict of interests among the editors.

Summary of Findings

Clinical Effectiveness of ulipristal acetate versus levonorgestrel

Two RCTs, Creinin 2006 and Glasier 2010, comparing the clinical effectiveness of ulipristal and levonorgestrel within 72 and 120 hours of unprotected intercourse respectively were included in the one moderate-quality[2] and one critically low-quality SR.[12] Ulipristal, 30 or 50 mg once, was associated with fewer pregnancies than levonorgestrel, 1.5 mg single- or split-dose according to the meta-analysis of the two RCTs with different follow-up lengths after intercourse. In the meta-analysis limited to the 72 hours of unprotected intercourse, ulipristal and levenorgestrel were associated with similar rates of pregnancy.[2] Ulipristal was also associated with lower likelihood of earlier return of menses and higher incidence of delayed return of next menses than levonorgestrel.[2] Shen et al. did not find evidence of a difference between the two medications with respect to side effects, including nausea, vomiting, spotting/bleeding after treatment, and overall abdominal pain.[2]

There were three meta-analyses included in the SR by Jatlaoui et al.[12] The two RCTs mentioned previously were included in the three meta-analyses and aimed to explore the effects of BMI on the clinical effectiveness of ulipristal and levonorgestrel.[12] Authors concluded that a BMI greater than or equal to 30 was associated with an increased risk of pregnancy after using levonorgestrel but not ulipristal for emergency contraception.[12]

Evidence-based guideline

The guideline published by the Society of Obstetricians and Gynaecologists of Canada, recommends initiating emergency contraception as soon as possible after unprotected intercourse and that timely access to all effective methods of emergency contraception

should be provided to Canadians.[7] Both ulipristal and levonorgestrel are effective up to five days after unprotected intercourse, however, ulipristal is more effective up to five days after unprotected intercourse, particularly when taken after 72 hours.[7] If taken on the day of ovulation or after ovulation, hormonal emergency contraception is not effective.[7] With respect to ulipristal, the guideline recommends that it should be the first choice for those with a BMI greater or equal to 25 and who prefer hormonal emergency contraception.[7] The guideline further states that BMI should not discourage the use of hormonal emergency contraception, but that copper IUDs are considered the most effective and should be recommended for those with a BMI greater or equal to 25 who are seeking emergency contraception.[7] Following the use of ulipristal, the use of back-up contraception or abstinence is recommended within the first five days and also within the first 14 days of beginning hormonal contraception.[7] It was stated that ulipristal and levonorgestrel should not be used together for emergency contraception.[7] Further, the guideline recommends that a pregnancy test should be ordered if there is no menstrual period within 21 days of using emergency contraception.[7]

Limitations

Although there were two SRs included, the evidence was based on two RCTs.[2,12] There were a limited number of primary studies comparing ulipristal and levonorgestrel. The scopes and populations of the SRs were not the same. The BMI categories in the subgroup analysis for ulipristal and levonorgestrel were not the same for ulipristal (BMI ≥ 30 kg/m^2 versus < 30) and levonorgestrel (BMI ≥ 30 kg/m^2 versus < 25).[12] It remained unclear about the role of different doses and BMI categories in the overall estimates.[2,12]

The development of the guideline by Black et al. was not clearly described, although it was endorsed by a professional association.[7]

Conclusions and Implications for Decision or Policy Making

For the comparative clinical effectiveness of ulipristal versus levonorgestrel for use as emergency contraception, two RCTs, Creinin 2006 and Glasier 2010, were synthesized in one moderate-quality[2] and one critically low-quality SR.[12] One evidence-based guideline for Canadian practitioners was identified.[7]

Ulipristal seems more effective than levonorgestrel to reduce the risk of pregnancy up to five days after unprotected inntercourse.[2] There was no evidence to show differences in the risks of adverse effects, including nausea and vomiting.[2]

With respect to BMI, the included SR with MA concluded that those with a BMI greater than or equal to 25 had an increased risk of pregnancy following levonorgestrel use but not ulipristal ECP use.[12] This corresponded to the guideline that indicates ulipristal should be recommended for those with a BMI equal to or greater than 25 who are seeking emergency contraception.[7] The guideline further suggests improving access to effective emergency contraceptive options in Canada. Due to the low volume of evidence and heterogeneity in the dosages, further research addressing ulipristal versus levonorgestrel may help to reduce uncertainty.

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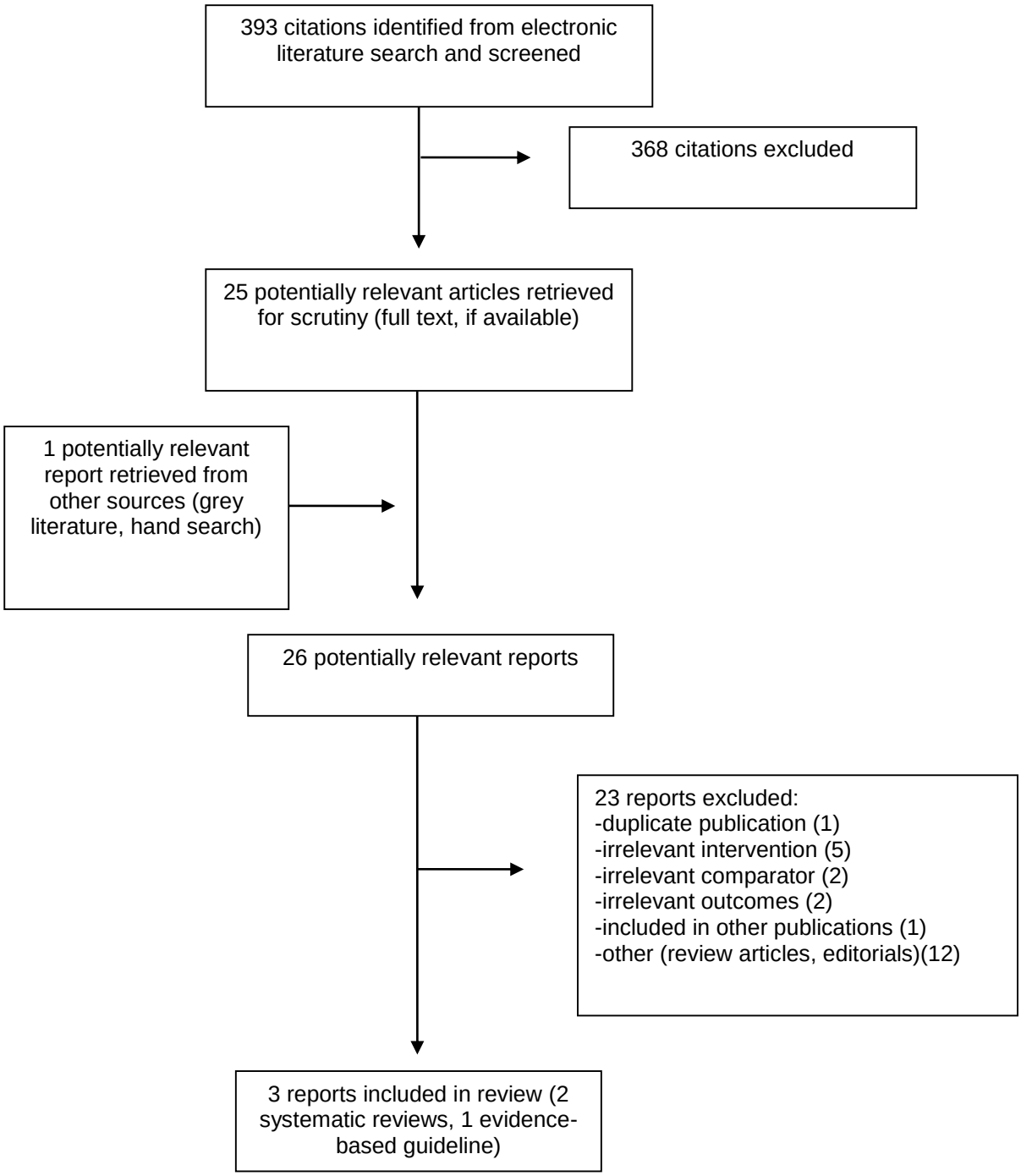
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Shen et al. 2017,[2] China	N = 115 2 RCT comparing ulipristal acetate and levonorgestrel (Creinin 2006 and Glasier 2010)	N = 60,479 in 11 studies using various emergency contraceptive methods N = 3,448 in 2 RCTs comparing ulipristal acetate and levonorgestrel as emergency contraception	Emergency contraception methods: ulipristal acetate, levonorgestrel, Yuzpe (estradiol-levonorgestrel combination),[a] mifepristone,[a] copper intrauterine device[a] Creinin 2006: levonorgestrel split-dose (0.75 mg each) versus ulipristal unmicronised, 50 mg single-dose, orally within 72 hours of unprotected intercourse Glasier 2010: levonorgestrel single-dose (1.5 mg once) versus ulipristal micronised, 30 mg, single-dose, orally within 120 hours of unprotected intercourse Both doses of ulipristal considered bioequivalent by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA, USA)	Numbers of pregnancies by risk status and time from intercourse, side effects, and menses
Jatlaoui et al. 2016,[12] USA	4 meta-analyses of 6 RCTs (4 publications) Among them, 3 meta-analyses relevant to this review (Glasier 2011, Kapp 2015, and Moreau and Trussell 2012) of 2 RCTs comparing ulipristal and levonorgestrel (Creinin 2006 and Glasier 2010)	N = 3,445 participants receiving emergency contraception with pregnancy status known afterwards in 2 RCTs [meta-analysis of Creinin 2006 and Glasier 2010 by Glacier et al. (2011)] N = 1,731 (a subset of the above-mentioned 3,445 in 2 RCTs) in the	Creinin 2006: levonorgestrel split-dose (0.75 mg each) versus ulipristal unmicronised, 50 mg single-dose, orally within 72 hours of unprotected intercourse Glasier 2010: levonorgestrel single-dose (1.5 mg once) versus ulipristal	Pregnancies by BMI categories, cut-offs including 25 and 30 kg/m^2

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	Inclusion criteria: "*primary research articles in all languages that identified the outcomes of pregnancy, ovulation or steroid hormone levels or serious adverse medical events among women with obesity using either levonorgestrel or ulipristal ECPs or combined oral contraceptives for the purpose of emergency contraception*" (p. 606)	meta-analysis by Kapp et al. (2015); reasons to select this subset not discussed N = 2221 in Glasier 2010, meta-analyzed by Moreau and Trussell (2012)	micronised, 30 mg, single-dose, orally within 120 hours of unprotected intercourse	

ECP = emergency contraception pill; RCT = randomized controlled trial

[a]not relevant to the current review

Table 3: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Chapter 3 of Black et al. 2015,[7] Canada						
Health care providers, Canadian practitioners Prepared by the Contraception Consensus Working Group and approved by the Executive and Board of the Society of Obstetricians and Gynaecologists of Canada	Emergency or post-coital contraception (Chapter 3): hormonal methods (levonorgestrel, ulipristal, and the Yuzpe regimen) and post-coital insertion of a copper intrauterine device	1. risks of pregnancy with different methods of emergency contraception (p. S21) 2. factors affecting effectiveness of emergency contraception pills	Databases: Medline and The Cochrane Database, in addition to grey literature search Time frame: published from January 1994 to January 2015 Studies for inclusion: systematic reviews, randomized control trials/controlled	Quality assessment tool: Report of the Canadian Task Force on Preventive Health Care	Not described	Not described

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
			clinical trials, and observational studies published in English Synthesis method: not described			

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[9]

Strengths	Limitations
Shen et al. 2017[2]	
- PICO criteria described - literature search with multiple databases, including PubMed and Cochrane database - PICO of included studies described - quality assessment of included studies using the Cochrane tool for assessing risk of bias - protocol published *a priori* (first published in 1998) - study selection criteria explained - study selection in duplicate - data extraction in duplicate - list of excluded studies provided - conflict of interest not declared - publication bias assessed for meta-analysis with 10 or more studies - meta-analysis using established methods	- sources of funding of the included studies not mentioned
Jatlaoui et al. 2016[12]	
- PICO criteria described - literature search with PubMed - PICO of included studies described - quality assessment of included studies using the US Preventive Services Task Force grading system - all primary research eligible for screening - conflict of interest not declared - include studies described in Table 1 - sources of funding of the included studies mentioned in Table 1 - risk of bias of the included studies described in Table 1 - conflict of interest declared: none	- protocol not published *a priori* - study selection not in duplicate - data extraction not in duplicate - list of excluded studies not provided - no meta-analysis due to heterogeneity - publication bias not assessed

PICO = population, intervention, comparator, and outcome

Table 5: Strengths and Limitations of Guidelines using AGREE II[10]

Item	Guideline
	Black et al. 2015[7]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Strongly agree
2. The health question(s) covered by the guideline is (are) specifically described.	Strongly agree
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Strongly agree

Item	Guideline
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Disagree
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Strongly disagree
6. The target users of the guideline are clearly defined.	Strongly agree
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Strongly agree
8. The criteria for selecting the evidence are clearly described.	Strongly disagree
9. The strengths and limitations of the body of evidence are clearly described.	Agree
10. The methods for formulating the recommendations are clearly described.	Strongly disagree
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Strongly disagree
12. There is an explicit link between the recommendations and the supporting evidence.	Strongly agree
13. The guideline has been externally reviewed by experts prior to its publication.	Strongly disagree
14. A procedure for updating the guideline is provided.	Strongly disagree
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Strongly agree
16. The different options for management of the condition or health issue are clearly presented.	Agree
17. Key recommendations are easily identifiable.	Strongly agree
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	Strongly agree
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	Agree
20. The potential resource implications of applying the recommendations have been considered.	Strongly disagree
21. The guideline presents monitoring and/or auditing criteria.	Strongly disagree
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Strongly disagree
23. Competing interests of guideline development group members have been recorded and addressed.	Strongly disagree

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Shen et al. (2017)[2]	
- Observed number of pregnancies: ulipristal, 50 or 30 mg, associated with fewer pregnancies than levonorgestrel, 1.5 mg single- or split-dose, after unprotected intercourse (RR = 0.59, 95% CI 0.35 to 0.99, 2 RCTs (one within 72 hours; the other within 120 hours), n = 3448, I2 = 0%, high-quality evidence) - Side effects: no evidence of a difference between the groups in rates of nausea, vomiting, headache, dizziness, fatigue, breast tenderness, diarrhoea, spotting/bleeding after treatment, overall abdominal pain, lower abdominal pain, upper abdominal pain, back pain or dysmenorrhea - Effects on menses: ulipristal associated with lower likelihood of earlier return of menses than levonorgestrel (RR 0.43, 95%CI 0.37 to 0.50, 2 RCTs, n = 3593, I2 = 72%, moderate quality evidence); ulipristal associated with higher incidence of delayed return of next menses than levonorgestrel (RR 1.65, 95% CI 1.42 to 1.92, 2 RCTs, n = 3593, I2 = 0%, high quality evidence) Sensitivity analysis based on the time from intercourse [Ulipristal acetate (all doses) versus levonorgestrel]: insignificant differences in all time intervals - Within 24 hours: RR = 0.40 (95% CI = 0.15 to 1.05, 2 studies) - 24 to 48 hours: RR = 1.33 (95% CI = 0.59 to 3.00, 2 studies) - 48 to 72 hours: RR = 0.34 (95% CI = 0.11 to 1.06, 2 studies) - 72 to 96 hours: RR = 0.23 (95% CI = 0.01 to 4.73, Glasier 2010) - 96 to 120 hours: RR = 0.32 (95% CI = 0.01 to 7.68, Glasier 2010) - 0 to 72 hours: 0.63 (95% CI = 0.37 to 1.07, 2 studies)	- "*Ulipristal acetate was associated with fewer pregnancies than levonorgestrel*" (p. 2)
Jatlaoui et al. (2016)[12]	
- Ulipristal: BMI ≥ 30 kg/m^2 was not significantly associated with pregnancy compared to those with a BMI < 25 kg/m^2 (OR = 2.62; 95% CI = 0.89 to 7.00) (meta-analysis in Glasier 2011) - Levonorgestrel: BMI ≥ 30 kg/m^2 associated with an increased risk of pregnancy, compared to a BMI < 25 kg/m^2 (OR = 4.4; 95% CI = 2.0 to 9.4) (meta-analysis in Glasier 2011) - Ulipristal or levonorgestrel: pregnancy associated with weight status (meta-analysis in Kapp 2015); both weight and BMI status associated with pregnancy (meta-analysis in Moreau and Trussell 2012)	- Effect sizes not compared between ulipristal and levonorgestrel. - Levonorgestrel: BMI ≥ 30 kg/m^2 associated with increased risk of pregnancy - Ulipristal: BMI ≥ 30 kg/m^2 not significantly associated with increased risk of pregnancy

CI = confidence interval; kg = kilogram; m = meter; OR = odds ratio; RCT = randomized controlled trial; RR = risk ratio

Table 7: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
Chapter 3 of Black et al. 2015[7]	
Summary Statements - "The copper intrauterine device is the most effective method of emergency contraception" - "A copper intrauterine device can be used for emergency contraception up to 7 days after unprotected intercourse provided that pregnancy has been ruled out and there are no other contraindications to its insertion" - "Levonorgestrel emergency contraception is effective up to 5 days (120 hours) after intercourse; its effectiveness decreases as the time between unprotected intercourse and ingestion increases" - "Ulipristal acetate for emergency contraception is more effective than levonorgestrel emergency contraception up to 5 days after unprotected intercourse. This difference in effectiveness is more pronounced as the time from unprotected intercourse increases, especially after 72 hours" - "Hormonal emergency contraception (levonorgestrel emergency contraception and ulipristal acetate for emergency contraception) is not effective if taken on the day of ovulation or after ovulation" - "Levonorgestrel emergency contraception may be less effective in women with a body mass index > 25 kg/m2 and ulipristal acetate for emergency contraception may be less effective in women with a body mass index ≥ 35 kg/m2 . However, hormonal emergency contraception may still retain some effectiveness regardless of a woman's body weight or body mass index" - "Hormonal emergency contraception is associated with higher failure rates when women continue to have subsequent unprotected intercourse" - "Hormonal contraception can be initiated the day of or the day following the use of levonorgestrel emergency contraception, with back-up contraception used for the first 7 days" -."Hormonal contraception can be initiated 5 days following the use of ulipristal acetate for emergency contraception, with back-up contraception used for the first 14 days" Recommendations - "*All emergency contraception should be initiated as soon as possible after unprotected intercourse*" - "*Women should be informed that the copper intrauterine device (IUD) is the most effective method of emergency contraception and can be used by any woman with no contraindications to IUD use*" - "*Health care providers should not discourage the use of hormonal emergency contraception (EC) on the basis of a woman's body mass index (BMI). The copper intrauterine device for EC should be recommended for women with a BMI > 30 kg/m2 who seek EC. If access and cost allow, ulipristal acetate for EC should be the first choice offered to women with a BMI ≥ 25 kg/m2 who prefer hormonal EC*" - "*Health care providers should discuss a plan for ongoing*	Summary Statements - II-2 - II-2 - II-2 - I - II-2 - II-2 - II-2 - III - III Recommendations - II-2A based on the ranking of the Canadian Task Force on Preventive Health Care - II-3A - II-2B

Recommendations	Strength of Evidence and Recommendations
contraception with women who use pills for EC and should provide appropriate methods if desired. Hormonal contraception should be started within 24 hours of taking levonorgestrel for EC, and back-up contraception or abstinence should be used for the first 7 days after starting hormonal contraception" - "*Women who use ulipristal should start hormonal contraception 5 days after using ulipristal. Ulipristal users must use back-up contraception or abstinence for the first 5 days after taking ulipristal and then for the first 14 days after starting hormonal contraception*" - "*Ulipristal acetate and levonorgestrel should not be used together for emergency contraception*" - "*A pregnancy test should be conducted if the woman has no menstrual period within 21 days of using pills or inserting a copper intrauterine device for emergency contraception*" - "*Health services should be developed to allow Canadian women to have timely access to all effective methods of emergency contraception*" (p. 938)	- III-B - III-B - III-B - II-B - III-A

EC = emergency contraception; IUD = intrauterine device; kg = kilogram; m = meter

Appendix 5: Overlap between Included Systematic Reviews

Table 8: Primary Study Overlap between Included Systematic Reviews

Primary Study Citation	Systematic Review Citation	
	Shen et al. 2017[2]	Jatlaoui et al. 2016[12]
Creinin 2006	X	X
Glasier 2010	X	X

X = included

Appendix 6: Additional References of Potential Interest

Reviews

Cleland K, Raymond EG, Westley E, Trussell J. Emergency contraception review: evidence-based recommendations for clinicians. *Clin Obstet Gynecol.* 2014;57(4):741-750.

Davis AR, Praditpan P. Emergency Contraception: Two Steps Forward, One Step Back. *Semin Reprod Med.* 2016;34(3):152-158.

Fok WK, Blumenthal PD. Update on emergency contraception. *Curr Opin Obstet Gynecol.* 2016;28(6):522-529.

Guidelines without systematic literature searches

Anonymous. Committee Opinion No. 707 Summary: Access to Emergency Contraception. *Obstet Gynecol.* 2017;130(1):251-252.

Guilbert E, Dunn S, Black A. Addendum to the Canadian Consensus on Contraception - Emergency Contraception: 1) Excluding pre-existing pregnancy when inserting copper IUD and 2) Initiation of hormonal contraception after emergency contraception. *Journal of Obstetrics & Gynaecology Canada: JOGC.* 2016;38(12):1150-1151.

Merki-Feld GS, Skouby S, Serfaty D, et al. European society of contraception statement on contraception in obese women. *Eur J Contracept Reprod Health Care.* 2015;20(1):19-28.

Schulz M, Goebel R, Schumann C, Zagermann-Muncke P. Non-prescription dispensing of emergency oral contraceptives: Recommendations from the German Federal Chamber of Pharmacists [Bundesapothekerkammer]. *Pharm Pract (Granada).* 2016;14(3):828.