Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy (Review)

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[Intervention Review]

Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy

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ABSTRACT

Background

Repeated use of postcoital hormonal contraception is not currently recommended due to the higher risk of side effects and lower contraceptive effectiveness compared to other modern methods of contraception. However, emerging evidence indicates renewed interest in a regular coitally-dependent method of oral contraception. We re-evaluated the existing data on safety and effectiveness of pericoital use of levonorgestrel and other hormonal drugs to prevent pregnancy.

Objectives

To determine the effectiveness and safety of repeated use of pre- and postcoital hormonal contraception for pregnancy prevention

Search strategy

We searched the computerized databases MEDLINE, POPLINE, CINAHL, LILACS, EMBASE and CENTRAL for trials that tested repeated pre- and postcoital use of hormonal drugs for pregnancy prevention. We also searched for current trials via ClinicalTrials.gov and ICTRP.

Selection criteria

Published and unpublished studies in any language of repeated postcoital or immediately precoital use of hormonal drugs for contraception with pregnancy as an outcome

Data collection and analysis

Two authors independently confirmed the eligibility and extracted data from the included studies. We calculated confidence intervals (CI) around individual study Pearl indices using a Poisson distribution. We presented individual study estimates and pooled estimates and their 95% CI, where appropriate.

Main results

We found 21 trials that evaluated pericoital use of LNG and other hormonal drugs on a regular basis to prevent pregnancy. Pericoital levonorgestrel (LNG) was reasonably efficacious and safe. The pooled Pearl Index for the 0.75 mg dose of LNG was 5.1 per 100 woman-years (WY) (95% CI 3.8 to 6.7). The pooled Pearl Index for all doses of LNG was 4.9 per 100 WY (95% CI 4.3 to 5.5). Other hormonal drugs appeared promising but most of them were not studied extensively. Most women liked the pericoital method in spite of frequent menstrual irregularities.

Authors' conclusions

The studies of pericoital LNG regimens provided promising results but had a number of serious methodological limitations. A pressing need exits to conduct a rigorous research to confirm the efficacy and safety of pericoital use of LNG as a primary means of contraception among women with infrequent intercourse. If the method is shown to be efficacious, safe and acceptable, the results may warrant revision of the current WHO recommendations and marketing strategies.

PLAIN LANGUAGE SUMMARY

Repeated use of hormonal drugs right before or after sex to prevent pregnancy

Currently, no oral birth control method is approved for using only when needed, i.e., at the time of sex. However, many women may want to use such a method. Our review looked at studies of different drugs taken around the sex act to find out how well the drugs worked to prevent pregnancy. We also assessed the safety of the drugs and whether women liked them.

We did computer searches to find relevant studies in all languages. We also wrote to researchers to find other trials. We assessed the quality of the research methods used in the studies. We entered the data into RevMan. The data were entered into RevMan and the Pearl Index was used to estimate effect.

We found 21 studies conducted over the past 40 years. These studies found that using some hormones right before or after sex did prevent pregnancy. In particular, levonorgestrel seemed to work well and was safe and accepted by thousands of women in several large trials. However, most of the studies were old and incomplete. More high quality research is needed before we can know for sure whether using levonorgestrel repeatedly around the time of sex is a good and safe method of birth control.

BACKGROUND

A coitally-dependent oral contraceptive may provide important advantages for women with infrequent sex as it reduces the dosing frequency, may be convenient and private. In addition, because pill ingestion is triggered by a coital event, its use may be more consistent than use of daily contraceptive pills. Postcoital contraception with oral levonorgestrel (LNG) was evaluated in numerous clinical studies and had been registered for decades in Eastern European and Asian countries (Seregely 1977; Farkas 1981). Currently, its repeated use as a regular contraceptive is not recommended due to the higher risk of side effects and lower contraceptive effectiveness compared to other modern methods of contraception (WHO 2000). The approved emergency contraceptive regimens are not intended for repeated use (ACOG 2005). However, repeated use of different drugs or other substances immediately before or after coitus as a primary method of contraception has been documented in several reports (Arowojolu 2000; Lerkiatbundit 2000; Britwum 2006). Although many of the reported methods are either untested drugs marketed for other purposes (e.g., norethindrone tablets) or are traditional preparations that are known to be ineffective, these data indicates an existing interest among women worldwide in pericoital oral method of contraception. Given the potential benefits and renewed interest in an oral coitally-dependent method of contraception, re-examination of the existing data on safety and effectiveness of pericoital use of hormonal drugs to prevent pregnancy is warranted. The results may help inform existing recommendations or provide guidance for future research.

Description of the intervention

Hormonal drug taken immediately before or after each act of intercourse for pregnancy prevention.

How the intervention might work

The main mechanism of action of a single use of emergency contraception appears to be prevention of ovulation. Effects on the endometrium, cervical mucus, embryo transfer and other components that contribute to the establishment of a viable pregnancy, are plausible but less well demonstrated (Croxatto 2003; Novikova 2007). Extrapolation of these data to the repeated use of pre- and postcoital hormonal contraception should be made only with caution.

Why it is important to do this review

Several non-comparative studies indicated that postcoital hormonal contraception is safe and effective when used repeatedly (WHO 1987; WHO 2000). Although randomized controlled trials may not have been conducted to date, a systematic review of the available observational clinical data may provide important guidance about whether the existing recommendation that warns against repeated use of the method should be reconsidered. A summary of the data may also be useful in planning future research.

OBJECTIVES

To determine the effectiveness and safety of repeated use of pre- and postcoital hormonal contraception for pregnancy prevention

METHODS

Criteria for considering studies for this review

Types of studies

We included all published and unpublished studies of repeated postcoital or immediately precoital use of hormonal drugs for contraception with pregnancy as an outcome. To be included in this review, written reports had to contain information on time of follow up, regimen and dose of the drug. Although we did not anticipate finding any comparative trials we searched and included all study designs. We followed the Cochrane guidance for inclusion of non-randomized trials (Higgins 2008). All languages of publication were eligible for inclusion.

Types of participants

We included all women who repeatedly used hormonal methods immediately before or after coitus to prevent pregnancy and who provided data in the eligible trials.

Types of interventions

Hormonal drug by mouth after or immediately before each act of intercourse and taken repeatedly during one or more menstrual cycles for contraception

Types of outcome measures

Primary outcomes

Pregnancy as defined by the researchers was the primary outcome of interest.

Secondary outcomes

All related side effects, including bleeding patterns, and discontinuation rates (if available) were the secondary outcomes.

Search methods for identification of studies

Electronic searches

We searched the computerized databases MEDLINE, POPLINE, CINAHL, LILACS, and EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) for trials that tested repeated pre- or postcoital use of hormonal drugs for pregnancy prevention. In addition, we searched for recent clinical trials through ClinicalTrials.gov (NIH 2008) and the International Clinical Trials Registry Platform (ICTRP) (WHO 2008).The strategies are given below.

MEDLINE via PubMed - two searches

1. (contraception, postcoital OR contraceptive agents, postcoital OR contraceptives, postcoital OR emergency contracept* OR postinor* OR “morning after pill” OR “morning after pills” OR vacation pills OR precoital OR pericoital OR (contracept* AND “plan b”) OR hormone* OR hormonal OR (contracept* AND (postcoital OR LNG))) AND (repeat* OR routine OR occasion* OR contraception behavior)
AND (clinical trial OR clinical trials OR randomized controlled trial OR randomized controlled trials OR controlled clinical trial OR controlled clinical trials OR random* OR evaluation studies OR comparative study OR follow-up study)
limited to female, human
2. (contraception, postcoital OR contraceptive agents, postcoital OR contraceptives, postcoital OR emergency contracept* OR postinor* OR “morning after pill” OR “morning after pills” OR vacation pills OR precoital OR pre-coital OR (contracept* AND “plan b”) OR ((contracept* OR hormone* OR hormonal) AND (postcoital OR post-coital OR post coital OR levonorgestrel OR norgestrel OR progestins OR d-norgestrol))) AND (repeat* OR routine OR occasion* OR continuous OR contraception behavior) AND (clinical trial OR clinical trials OR randomized controlled trial OR randomized controlled trials OR controlled clinical trial OR controlled clinical trials OR random* OR evaluation studies OR comparative study OR follow-up study)

POPLINE - three searches

1. (contraceptive agents, postcoital/ emergency contracept* /postinor*/"morning after pill/ morning after pills/ plan b) & (repeat* / routine/ occasion*) & contraceptive usage
AND
KW - qualitative
2. (contraceptive agents, postcoital/ emergency contracept* /postinor*/"morning after pill/ morning after pills/ plan b) & (repeat* / routine/ occasion*)
AND
KW- (behavior/contraceptive usage) & clinical trials
3. precoital

CENTRAL

contracept* AND (postcoital OR levonorgestrel OR emergency OR plan B OR morning after) in Title, Abstract or Keywords
AND repeat* OR routine OR occasion* OR contraception behavior in Title, Abstract or Keywords
OR postinor OR precoital OR pre-coital in Title, Abstract, or Keywords

CINAHL - two strategies

1. contraception, postcoital or contraceptive agents, postcoital or contraceptives, postcoital or emergency contracept* or postinor* or "morning after pill" or "morning after pills" or "vacation pills" or (contracept* and "plan b") or (contracept* or hormone* or hormonal)
and (postcoital or post-coital or "post coital" or levonorgestrel or norgestrel or progestins or d-norgestrol)
and repeat* or routine or occasion* or continuous or contracept* behavior
not human or female*
2. contraception, postcoital or contraception, precoital or contraceptive agents, postcoital or contraceptive agents, precoital or contraceptives, postcoital or contraceptives, precoital or emergency contracept* or postinor* or "morning after pill" or "morning after pills" or "vacation pills" or (contracept* and "plan b")
or (contracept* or hormone* or hormonal) and (postcoital or precoital or post-coital or pre-coital or "post coital" or "pre coital" or levonorgestrel or norgestrel or progestins or d-norgestrol)
and repeat* or routine or occasion* or continuous or contracept* behavior
not human or female*

LILACS

precoital or contraception, postcoital or contraceptive agents, postcoital or contraceptives, postcoital or anticoncepcion postcoital or anticoncepcao pos-coito or anticonceptivos poscoito or anticoncepcionais pos-coito or emergency contracept$ or postinor$ or "morning after pill" or "morning after pills" or "vacation pills" or (contracept$ and "plan b") [Words]

EMBASE

((contraceptive agent or contraceptive()agent or oral contraceptive agent or hormonal contraception or emergency()contraceptive()pill or emergency contracept?
or postinor or morning()after()pill? or vacation()pill? or contracept? and plan()b)
and
(precoital or precoitally or precoitus or precoit?)
not animal)
OR
((levonorgestrel or norgestrel or progestins or d-norgestrol or contracept? or hormone? or hormonal)
and(repeat? or routine or occasion? or continu? or contracepti? ()behavior)
and(precoital or precoitally or precoitus or precoit?))

ClinicalTrials.gov

Search terms: (postcoital OR precoital OR levonorgestrel OR emergency OR plan B OR morning after) AND (repeat* OR routine OR occasion* OR contraception behavior)
Intervention: contraception

ICTRP

Title: postcoital OR precoital OR levonorgestrel OR emergency OR plan B OR morning after
Intervention: contracept

Searching other resources

We examined the reference lists of relevant articles. We contacted experts in the field for information about any published or unpublished trials not discovered in our search.

Data collection and analysis

Selection of studies

Two authors independently reviewed the search results for reports potentially eligible for inclusion.

Data extraction and management

The first author extracted and entered the data from non-randomized trials in RevMan 5 into 'Additional tables', and described the results in the text. Another author performed a second, independent data abstraction and verified the initial data entry for accuracy. Any discrepancies were resolved by discussion.

Assessment of risk of bias in included studies

We used the principles outlined in section 13.5 of the Cochrane handbook for interpretation of the non-randomized data (Higgins 2008). Limitations in design were summarized in the text and in the 'Risk of bias' section in Characteristics of included studies, and were considered when interpreting the results.

Measures of treatment effect

The majority of the trials measured treatment effect by Pearl index (number of pregnancies per 100 woman-years (WY) of use). For studies not reporting the Pearl index, we calculated it based on the available data, assuming conservatively that 13 reported cycles were equivalent to one year. Four trials calculated WY by assuming that there are 12 cycles per year (Canzler 1984; He 1991; Moggia 1974; Rubio 1970). Two trials excluded 4% of treated women (those with protocol violations) from the analysis. In one case, the researchers reported that the 11 excluded women had no pregnancies, so we were able to recalculate the pregnancy rate including those women (WHO 1987), but in the other case, the outcomes in the 65 excluded women were not reported (He 1991). One trial included only pregnancies that occurred during perfect method use in the Pearl calculations (Zanartu 1976). In two trials, the efficacy figure provided by the researchers was not reproducible from the data in the report (Sas; Schering 1978). We recalculated Pearl indices for these eight reports, as well as for four studies that did not provide Pearl index statistics at all, and presented them separately. We used the most conservative (i.e., highest) estimate of the original and recalculated estimates for the pooled pregnancy rates and for our conclusions.

In addition to pregnancy rates during typical (i.e., any) use of the method, several researchers also reported failure rates that ostensibly occurred only during perfect use of the method (Canzler 1984; Larranga 1975; Seregely 1982). However, in calculating these rates, they used all months of method use in the denominator rather than just months of perfect use, a common mistake in this type of calculation (Trussell 2004). As a result, the reported perfect use rates are inaccurately low and therefore were not included in this review

Dealing with missing data

For studies conducted within the last 10 years, we attempted to contact researchers for missing data and clarification of issues related to participants and methods.

Assessment of heterogeneity

The study populations, designs and outcomes were heterogeneous. We described both the clinical and methodological diversity of the studies. Clinical diversity included differences in participants, interventions, and outcomes, while methodological diversity addressed study design and limitations of design and implementation. We did not perform a formal meta-analysis due to the lack of comparative data. Hence, we did not evaluate the effect of statistical heterogeneity on the outcomes.

Data synthesis

We calculated confidence intervals (CI) around individual study Pearl indices using a Poisson distribution. We presented individual study estimates and pooled estimates and their 95% CI, where appropriate. We discussed the results according to the quality of evidence (Higgins 2008). The safety and acceptability outcomes varied among the studies. Therefore, we neither tabulated nor conducted meta-analysis of the safety and acceptability outcomes.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 21 trials that evaluated contraceptive effectiveness of repeated pre- and postcoital use of hormonal drugs. These trials included 12,332 women in Europe, Asia, and Central and South America. Although nine of the studies evaluated more than one hormone regimen, we considered each arm of these studies separately, for reasons explained in Risk of bias in included studies.

- Nine trials investigated postcoital use of a tablet containing LNG 0.75 mg (Chernev 1995; He 1991; Klawe 1984; Kliment 1986; Nirapathpongporn; Sas; Seregely 1982; WHO 1987; WHO 2000);
- Four trials evaluated postcoital use of LNG in one or more doses other than 0.75 mg (Echeverry 1974; Kesseru 1973; Larranga 1975; Schering 1978);
- Six trials evaluated pericoital use of one or more hormones other than LNG (Cox 1968; Mischler 1974; Rubio 1970; Szontagh 1969; Zanartu 1974; Zanartu 1976);
- One trial evaluated postcoital use of a different hormonal drug and a dose of LNG other than 0.75 mg (Moggia 1974);
- One trial studied a) postcoital use of LNG 0.4 mg and b) LNG 0.75 mg as a divided dose pre- and postcoitally (Canzler 1984).

Included studies

The included studies are briefly described below. In this review, we discuss each arm of Moggia 1974 and Canzler 1984 separately, with studies of comparable drugs and doses. Additional details can be found in Characteristics of included studies.

LNG 0.75 mg

Ten studies evaluated pregnancy rates, discontinuation, side effects, including bleeding abnormalities, and acceptability in women using LNG 0.75 mg pericoitally. The specific use instructions for the pill use varied across the trials. He 1991 and WHO 1987 evaluated one tablet of LNG 0.75 mg taken repeatedly during the periovulatory period of one cycle as soon as possible after the first coitus and no later than 8 hours after; second tablet was taken 24 hours later regardless of whether another coital exposure had occurred during that time. Canzler 1984 administered LNG 0.5 mg prior to, and LNG 0.25 mg eight hours after, intercourse (a total of 0.75 mg per intercourse). Chernev 1995 evaluated one tablet of LNG 0.75 mg taken immediately (within one hour) after an unprotected intercourse. Other trials studied postcoital administration of one tablet of LNG 0.75 mg with slight variations in the instructions for additional pill intake in case of repeated intercourse (Klawe 1984; Kliment 1986; Nirapathpongporn; Sas; Seregely 1982; WHO 2000). Some of these instructions were complex, unclear, or vague; for example, in one study, women were told that after repeated coitus, they should 'possibly' take a tablet the next day (Kliment 1986). More details on pill regimens can be found in Characteristics of included studies.

Doses other than LNG 0.75 mg

Six studies evaluated pregnancy and side effects in women using LNG postcoitally in doses other than 0.75 mg. Echeverry 1974 studied LNG 1 mg taken within eight hours after intercourse. Kesseru 1973 tested five doses of LNG (0.15, 0.25, 0.30, 0.35 and 0.40 mg) taken immediately (but no later than three hours) after intercourse. Larranga 1975 evaluated LNG 1 mg and Schering 1978 examined LNG 0.6 mg taken immediately after intercourse. Canzler 1984 evaluated LNG 0.4 mg taken within 12 hours after intercourse. Moggia 1974 studied LNG 0.35 mg taken within one hour after intercourse.

Hormones other than LNG

Seven trials evaluated pericoital use of hormones other than LNG. Cox 1968 evaluated pregnancy rates and side effects of precoital use of megestrol acetate 0.5 mg (a progestagen). Szontagh 1969 evaluated postcoital use of dienoestrol (an estrogen) in 10 women and dienoestrol combined with ethynodiol-diacetate in 20 other women. Rubio 1970 and Mischler 1974 evaluated postcoital use of different doses of quingestanol acetate (a progestagen). These two reports included some overlapping data, which we included only once in this review. Two studies included both pericoital and daily treatments (Zanartu 1974; Zanartu 1976). Given the purpose of this review, we excluded the daily treatment regimens from these two studies from further discussion. Moggia 1974 evaluated postcoital use of quingestanol acetate 1.5 mg taken within one hour after intercourse.

Excluded studies

We excluded 10 trials from our analysis. Four reports did not contain information on treatment regimen (Hetenyi 1988; Kulakov 1983; Szczurowicz; Unzeitig 1989). Two reports did not provide either pregnancy rates (Pearl indices) or sufficient data to allow us to calculate them (Krymskaya 1983; Serov 1983). One trial did not report pregnancy outcome (Orley). Another trial (Vasilev 1983), originally published in Bulgarian, was excluded after several attempts to have it translated. Two studies were excluded because we could not locate their full reports (published or unpublished), and the information provided in the abstract (Hurtado 1975) and incomplete report (Czekanowski) were insufficient to evaluate the quality of the studies and analyze the results.

Risk of bias in included studies

Methodological limitations of the included studies are summarized below. Additional details can be found in the Characteristics of included studies. We followed the standard risk of bias format for RCTs although not all factors that may affect the quality of a RCT are relevant for an observational study.

The results of 12 trials were published in peer-reviewed journals (Canzler 1984; Cox 1968; He 1991; Kesseru 1973; Kliment 1986; Larranga 1975; Mischler 1974; Moggia 1974; Rubio 1970; WHO 1987; WHO 2000; Zanartu 1974). The results of one study were published in a manuscript (Zanartu 1976). Four trials were published in journals for which we could not establish the peer-review status (Chernev 1995; Klawe 1984; Seregely 1982; Szontagh 1969). Four unpublished reports were assessed for quality and included in the review (Echeverry 1974; Nirapathpongporn; Sas; Schering 1978), two of these were undated. Two trials were published in another language and translated into English (Canzler 1984; Kliment 1986).

The dates of data collection were not reported in most of the reports. Most of the trials were conducted during the 1970s and 1980s, and the quality of reporting was poor. Eleven studies were designed as case series, or prospective non-comparative trials (Chernev 1995; Echeverry 1974; Klawe 1984; Kliment 1986; Larranga 1975; Nirapathpongporn; Sas; Schering 1978; Seregely 1982; WHO 1987; WHO 2000). Nine other trials included multiple groups of women given different treatment regimens or instructions for use; the method of treatment allocation was not described (and we presume was not randomized). Most of these

reports had no formal (statistical) comparisons of the treatments studied, and provided insufficient data for assessing confounding or other biases. Therefore, we considered each group in these nine multi-arm studies as a separate case-series. We found only one randomized trial that compared tablets produced in two different countries, but that contained the same dose of active ingredient administered in the same way (He 1991). Since this randomized comparison did not address our main research question, we did not evaluate its quality as a randomized trial. Because the study found no difference in the estimates of treatment effect between the two groups, we combined their results.

Thus, all the data in this review are presented as if they came from non-comparative studies. Our findings are limited to absolute estimates of pregnancy rates among women using the methods studied.

Incomplete outcome data

Six of the 21 reports specified an intended duration of method use (Table 1). In the three studies in which this duration was less than six months, all women treated completed the intended use period (He 1991: WHO 1987; Szontagh 1969). In the other three studies, in which the intended duration of method use was 6 months (Chernev 1995; WHO 2000) or 10 months (Nirapathpongporn), 33% to 67% of participants used the method for the intended use period. Two of these study reports cited both the number of women who were known to have discontinued method during observation and the number who were lost to follow up. In WHO 2000, only 4% of participants were lost by 6 months; in Nirapathpongporn, 49% were lost by 10 months. The study with the lowest completion rate (33% at six months) did not provide data separately on the proportions of women who discontinued early or were lost (Chernev 1995).

Table 1. Continuation of treatment

Study	N	Intended duration of use*	Lost to follow up (n) %	Discontinued without pregnancy (n) %	Used ≥ 6 months (n) %	Range for duration of use*	Mean duration of use*
LNG 0.75 mg							
Canzler 1984	27	---	56%**		---	3 to 17	8.4
Chernev 1995	120	6	---	---	(40) 33%	---	4.8
He 1991	361	1	(0)	(0)	(0)	1	1
Klawe 1984	32	---	---	---	---	11	9.3
Kliment 1986	40	---	---	---	---		6
Nirapathpongporn	129	10	(63) 49%	(14) 11%	(55) 43%	1 to 15	5.2
Sas	50	---	---	---	(8) 16%	2 to 12	4.2
Seregely 1982	1315	---	15% to 20%	(97) 7%	---	---	6.7
WHO 1987	259	1	(0)	(0)	(0)	1	1
WHO 2000	295	6	(13) 4%	29%†	67%†	---	5.4

Table 1. Continuation of treatment (*Continued*)

LNG doses other than 0.75 mg							
Canzler 1984	77	---	60%**		---	3 to 36	13.1
Echeverry 1974	127	---	52%**		---	---	4.4
Kesseru 1973	4631	---	10% to 17%‡	25% to 31%‡	42% to 78%‡	Up to 30	9
Larranga 1975	298	---	(106) 36%	(64) 22%	(189) 63%	1 to 16	8.7
Moggia 1974	314	---	(17) 5%	(34) 11%	(115) 37%	1 to 26	13.6
Schering 1978	340	---	37%**		73%	---	9.2
Drugs other than LNG							
Cox 1968	47						14.2
Mischler 1974	2175						4.8
Moggia 1974	585		(35) 6%	(508) 87%	(405) 69%	1 to 20	8.1
Rubio 1970	441					up to 14	4.2
Szontagh 1969	30	3 or 5	(0)	(0)	(0)	3 or 5	3 or 5
Zanartu 1974	333						5.5
Zanartu 1976	306		(27) 9%	(31) 10%			5.4

*Months or cycles (as presented in report)
**Lost to follow up and early discontinuation rates are combined
†Approximate; based on estimates in report
‡Range across 5 study groups

Two reports did not specify an intended duration of follow up but nevertheless presented detailed information about continuation, discontinuation, and loss to follow up in each month or three-month periods. In one of these trials, 68% of women completed at least six months of use, and 11% were lost to follow up in that time (Kesseru 1973). In the other trial, the corresponding figures were 60% and 27% (Larranga 1975).

The other 13 reports did not include sufficient information to allow an assessment of the completeness of outcome data ascertainment. Loss to follow up may result in underestimation of the pregnancy rates during method use because women who were lost

may have had undetected pregnancies while still using the method after the last study contact.

Selective reporting

All trials included in this review clearly defined their main objectives and interventions, although some trials lacked clear description of the drug regimen or how the drug was dispensed to participants. Only seven studies clearly specified the main study outcomes (Canzler 1984; He 1991; Kesseru 1973; Moggia 1974; Seregely 1982; WHO 2000; Zanartu 1976). Based on these seven reports as well as on the reported results in other trials, pregnancy and side effects including bleeding problems were the main study outcomes in all included trials. In addition, several studies evaluated continuation rates and reasons for discontinuation (Echeverry 1974; Kesseru 1973; Larranga 1975; Moggia 1974; Nirapathpongporn; Schering 1978; WHO 1987; WHO 2000; Zanartu 1976). One trial evaluated acceptability through a questionnaire in addition to measuring discontinuation (WHO 2000). Most studies lacked detailed description of the trial procedures. Only nine reports mentioned the frequency of follow-up contacts. Only one study specified how pregnancy was ascertained (He 1991). Although menstrual irregularities were one of the main outcome in all trials, only nine trials reported on how the data on bleeding patterns were collected and evaluated (Canzler 1984; Echeverry 1974; He 1991; Larranga 1975; Moggia 1974; Seregely 1982; WHO 2000; Zanartu 1974; Zanartu 1976).

Other potential sources of bias

Only 13 reports specified inclusion and exclusion criteria (Canzler 1984; Echeverry 1974; He 1991; Kesseru 1973; Klawe 1984; Mischler 1974; Nirapathpongporn; Rubio 1970; Seregely 1982; WHO 1987; WHO 2000; Zanartu 1974; Zanartu 1976). Some of these reports failed to clearly define these criteria; for instance, two studies included only 'fertile' women but did not explain how fertility was assessed. The uniformity of subjects' characteristics in some studies suggested that additional unstated criteria may also have been used. Nine studies (Chernev 1995; Cox 1968;Larranga 1975; Moggia 1974; Sas; Schering 1978; Szontagh 1969; Zanartu 1974; Zanartu 1976) did not specify any eligibility criteria for the study. The descriptions of the study populations in some studies are unclear and are limited or nonexistent.

Six studies had sample sizes of less than 100 women (Canzler 1984; Cox 1968; Szontagh 1969; Klawe 1984; Kliment 1986; Sas), whereas three included more than 1000 women (Kesseru 1973;Mischler 1974; Seregely 1982). As previously noted, two trials had large sample sizes but short duration of follow up (one treatment cycle), which limited the exposure to both pregnancy and the drug (He 1991; WHO 1987).

A few reports commented on possible relations between the treatment effect and dose, coital and dosing frequency, duration of treatment and time elapsing between coitus and pill intake. Canzler 1984 evaluated potential role of the dose, coital frequency, time after coitus, duration of medication and number of tablets taken; Kesseru 1973 explored length of treatment, coital frequency and number of pills taken; Schering 1978 assessed the possible role of duration of treatment; Rubio 1970 evaluated the dose; and Mischler 1974 evaluated both the dose and number of pills taken per cycle. However, none of these associations were evaluated rigorously (statistically). Also, some such associations noted may be spurious. For example, an association between the number of tablets taken per cycle and the likelihood of side effects in a cycle may simply reflect the fact that women are more likely both to take more tablets and to have side effects in long cycles than in short cycles.

Most of the trials evaluated compliance with the treatment regimen and distinguished the results as drug or method failure. However, only seven trials described their methods of collection of adherence data (Canzler 1984; Echeverry 1974; He 1991; Larranga 1975; Moggia 1974; Seregely 1982; WHO 2000).

All studies evaluating doses of LNG other than 0.75 mg were sponsored by Schering AG (Echeverry 1974; Kesseru 1973; Larranga 1975; Moggia 1974). Canzler 1984 was co-sponsored by another pharmaceutical company, VEB Jenapharm. The largest Hungarian trial to support introduction of LNG 0.75 mg for regular postcoital contraception was sponsored by its manufacturer, the pharmaceutical company Gedeon Richter, Ltd. (Seregely 1982).Three multicenter trials of LNG 0.75 mg for regular postcoital contraception were sponsored by WHO (He 1991; WHO 1987; WHO 2000); Gedeon Richter, Ltd. provided pills for WHO 2000. In two trials, pills were provided by the pharmaceutical manufacturers but the trials were sponsored by the University of Chile (Zanartu 1974; Zanartu 1976).

Effects of interventions

LNG 0.75 mg

The 10 studies of the LNG 0.75 mg dose were conducted in numerous countries in Europe and Asia, and two multicenter studies had sites in Cuba. The evaluated regimens of the drug were slightly different (Characteristics of included studies).

The characteristics of the study populations varied considerably. Most of the trials had no age restriction or admitted a wide range of ages, but three enrolled only young (Canzler 1984; Chernev 1995; Seregely 1982) or only older women (Klawe 1984). In some studies, all participants met stringent criteria to demonstrate fertility, such as evidence of ovulation in prior cycles, or previous pregnancy with the current partner (Canzler 1984; He 1991; Kliment 1986; Nirapathpongporn; Sas; WHO 1987; WHO 2000), and some trials excluded women who had recently used hormonal contraceptives or who had a history of pelvic inflammatory disease (He 1991; WHO 1987; WHO 2000). Other trials admitted women with no evidence of fertility. Most of the trials excluded women

who expected to have high coital frequency during the trial: in three trials the limit was four acts of sexual intercourse a month (Klawe 1984; Seregely 1982; WHO 2000), whereas others used a more general rule like "irregular" or "casual" or "infrequent" sex (Kliment 1986; Nirapathpongporn; Sas). Two trials did not limit coital frequency as their objective was to evaluate women at higher risk of conception (He 1991; WHO 1987). Canzler 1984 enrolled women who had up to 10 acts of sexual intercourse a month.

The studies evaluating pericoital use of LNG 0.75 mg included a total of 2628 women. The studies reported the duration of use of the method in cycles, months, or WY. If cycles and months were combined, the total number of such intervals in these studies was 13,240. Thus the average duration of use per subject was five cycles or months. However, two studies were designed to allow only one cycle of treatment (He 1991; WHO 1987). If those studies were excluded, the average duration of method use per subject was 6.3 cycles or months. Additional details on duration of treatment can be found in Table 1.

Coital frequency in these trials ranged from 1 to 15 acts per month or cycle. Average coital frequency in the eight studies that reported these data was about 4 acts per month or cycle, ranging from 2 to 7.5. More data on coital frequency and pill intake observed during the trial are presented in Table 2.

Table 2. Coital frequency and tablet taking by study

Study	Sex acts per cycle or month, mean (range)	Sexual acts, total	Pills per cycle or month, mean (range)	Pill intake, total
LNG 0.75 mg				
Canzler 1984	3.4	---	3.4 (1 to 16)	---
He 1991	3.2 (1 to 9)	---	4.3 (2 to 7)	---
Kliment 1986	2.2	---	---	---
Nirapathpongporn	4.08	---	4.07 (0 to 10)	---
Sas	4.3	850	---	---
Seregely 1982	4 (1 to 8)	27,253	---	---
WHO 1987	7.5	---	4.0 (0 to 7)	---
WHO 2000	4.1*	6509	4.0*	6384
Doses other than LNG 0.75 mg				
Canzler 1984 (0.4 mg dose)	4.5	---	4.5 (1 to 15)	---
Echeverry 1974	6.3*	3519	6.3*	3519
Kesseru 1973	8.0	---	---	---
Larranga 1975	---	---	7.9*	20,153
Moggia 1974 (0.35 mg group)	8	---	---	---

Table 2. Coital frequency and tablet taking by study (*Continued*)

Schering 1978	(7 to 12)	---	(7 to 12)	---
Hormones other than LNG				
Cox 1968	10*	---	10*	---
Rubio 1970 (quingestanol acetate 0.5 mg)	---	---	10.5*	
Mischler 1974 (quingestanol acetate by dose)				
0.5 mg	---	---	8.9	---
0.6 mg	---	---	8.7	---
0.75 mg	---	---	8.1	---
0.8 mg	---	---	10.6	---
1.5 mg	---	---	7.9	---
2.0 mg	---	---	7.8	---
Moggia 1974 (quingestanol group)	8	---	---	---

No relevant data were available from Chernev 1995, Klawe 1984, Szontagh 1969, Zanartu 1974, and Zanartu 1976.
*Estimated using the available data

Efficacy

All regimens of LNG 0.75 mg when taken repeatedly after unprotected coitus resulted in low or moderate Pearl indices ranging from zero to 18.6 per 100 WY (Table 3). Three large well-designed multi-center clinical trials with a total of 915 women appeared to be of good methodological quality: they were all published in peer-reviewed journals, and the inclusion criteria, trial procedures, and intended duration of follow up were clearly defined (He 1991; WHO 1987; WHO 2000). The reported pregnancy rates in these three trials ranged from 6.8 to 18.0 pregnancies per 100 WY, resulting in a pooled Pearl index of 8.9 per 100 WY (95% CI 5.1 to 14.4). The addition of the other seven trials decreased the pooled pregnancy rate by nearly half (5.1 per 100 WY; 95% CI 3.8 to 6.7). As previously noted, the quality of the latter studies was not often clear, due to reporting limitations (Risk of bias in included studies). Details of each study can be found in Characteristics of included studies.

Table 3. Number of pregnancies and Pearl index in studies of LNG 0.75 mg

Study	Presented in original source				Calculated by authors		Used by authors in calculating pooled rates	
	N	Cycles	Pregnancies	Pearl index	Woman-years*	Pearl index	Pearl index	95% CI

Table 3. Number of pregnancies and Pearl index in studies of LNG 0.75 mg (*Continued*)

Canzler 1984	27	226	2	10.6	17.4	11.5	11.5	1.4 to 42.5
Chernev 1995	120	570	4	---	43.8	9.1	9.1	2.5 to 23.4
He 1991	361	361	5	16.6	27.8	18.0	18.0	5.8 to 42.0
Klawe 1984	32	297	0	---	22.8	0	0	0 to 16.2
Kliment 1986	40	240	1	---	18.5	5.4	5.4	0.1 to 30.1
Nirapath-pongporn	129	667 (months)	4	---	55.6	7.2	7.2	2.0 to 18.4
Sas	50	209	3	11.5	16.1	18.6	18.6	3.8 to 54.5
Seregely 1982	1315	8815	23	3.37	678.1		3.4	2.2 to 5.1
WHO 1987	259	259	2	10	20.8	9.6†	10.0	1.2 to 36.0
WHO 2000	295	1596‡ (months)	9	6.8	133‡		6.8	3.1 to 12.9

*Calculated assuming 13 cycles/year
†Recalculated with 11 women excluded from original analysis after treatment
‡Report presented woman-years; authors calculated months

Pregnancies occurred in 9 out of the 10 trials that evaluated pericoital use of LNG 0.75 mg. Two out of these nine trials did not provide information on treatment adherence (Chernev 1995; WHO 2000). The other seven trials reported a total of 40 pregnancies; 26 (65%) were classified by the researchers as user failure, a possible indication of the complexity of the pill instructions.

Safety and acceptability

In all studies the main reported side effect was menstrual irregularity. A few studies reported reduced or increased amount or duration of flow (Sas; Seregely 1982; WHO 2000). One study reported "severe menstrual bleeding" in 5/570 cycles (Chernev 1995). None of the studies measured hematologic indices.

The studies provided no consistent evidence regarding a possible relationship between bleeding abnormalities and either frequency of pill intake or total dose of the drug. Two reports (Canzler 1984; Chernev 1995) suggested that side effects including cycle control were worse in women who took more tablets per cycle, but as noted previously, this association may be spurious. Three reports specifically noted no association between cycle control and frequency of the drug dosing (He 1991; Nirapathpongporn; WHO 1987). One study found a decrease in bleeding irregularities with duration of use of the method, but that may have been due to early attrition of subjects who experienced these problems (Nirapathpongporn). No serious adverse events were reported. Non-menstrual side effects were infrequent and included nausea, breast tenderness, dizziness, lower abdominal pain, fatigue, headache, weight gain, irritability, weakness, headache and loss of libido. Because of variable reporting, the incidence of these complaints could not be combined across studies. Most researchers indicated that non-menstrual side effects were clinically insignificant. No consistent relationship was apparent between incidence of side effects and treatment frequency or dose (He 1991, WHO 1987).

Discontinuation due to side effects was apparently uncommon. In two studies that aimed to follow women for 6 months (WHO 2000) and 10 months (Nirapathpongporn), 15% and 3% of all enrolled participants, respectively, discontinued within those time periods because of bleeding abnormalities. In a study of 1315 women who used the method for an average of 6.7 months, only 3% of all enrolled participants stopped using the method because of side effects (Seregely 1982).

Limited data on pregnancy outcomes were available from the LNG 0.75 mg trials. Seregely 1982 reported that 21 out of the 23 study pregnancies were interrupted, and two full-term delivered babies were healthy. No abnormal pregnancies were reported in other studies, but whether women in these studies were followed beyond the onset of pregnancy is unclear.

The method was well accepted by participants. One trial noted that 65.8% of participants were "in favor of" the method whereas only 19.3% said that they were opposed to it (WHO 2000). Another found that 49% of those who completed the intended follow-up period without pregnancy were satisfied with the method (Nirapathpongporn). In spite of its good acceptability reported by most of the trials, some researchers recommended that it should not be widely promoted because of lower efficacy than other methods, high incidence of bleeding abnormalities, high total dose of hormone, and lack of protection from sexually transmitted infections (WHO 2000).

Doses other than LNG 0.75 mg

Six studies evaluated doses of LNG other than 0.75 mg. One study included five groups of women who received doses between 0.15 mg and 0.40 mg. The other five studies assigned women to only one dose of LNG (ranging from 0.35 mg to 1.0 mg) taken within a few hours after unprotected intercourse. In one trial, only one dose was recommended for any eight-hour interval (Echeverry 1974). See Characteristics of included studies for more detail.

Inclusion criteria for most of these trials were much less stringent than for the trials of 0.75 mg tablets. None of the studies had a specific age restriction. In five of the trials all subjects were parous, and in the other trial (Canzler 1984), all had biphasic menstrual cycles, suggesting the occurrence of ovulation. However, in three studies some or most subjects were enrolled immediately postpartum or when lactating (Echeverry 1974; Larranga 1975; Moggia 1974). One study enrolled women who expected to have sex up to 10 times per month (Canzler 1984). Other trials enrolled women without regard to expected coital frequency.

The six trials included 5787 subjects who used the method for a total of 53,347 cycles or months. The mean duration of use was thus 9.2 cycles or months per subject. The maximum duration of use in these trials ranged from 12 to 36 months. More details on duration of treatment can be found in Table 1. Coital frequency in these trials was higher than in the trials of LNG 0.75 mg. The available results on coital frequency and pill intake after admission to the trial are presented in Table 2. In most studies, the reported number of tablets taken was concordant with coital frequency, suggesting compliance with the assigned regimen.

Efficacy

The Pearl indices ranged from zero to 9.0 pregnancies per 100 WY, except among the 28 subjects in the five-dose study assigned to the lowest dose, who yielded a much higher figure (45.2 per 100 WY) (Table 4). Combining these six studies with the data from the trials of the LNG 0.75 mg dose, we estimated an overall Pearl index for all doses of LNG of 4.9 per 100 WY (95% CI 4.3 to 5.5).

Table 4. Number of pregnancies and Pearl index in studies of LNG doses other than 0.75 mg

Study	Presented in original source				Calculated by authors		Used by authors in calculating pooled rates	
	N	Months	Pregnancies	Pearl index	Woman-years*	Pearl index	Pearl index	95% CI
Canzler 1984	77	1011 (cycles)	7	8.3	77.8	9.0	9.0	3.6 to 18.5
Echeverry 1974	127	557 (cycles)	0		42.8	0	0	0 to 8.6
Kesseru 1973 by dose								
0.15 mg	28	239	9	45.2	19.9			

Table 4. Number of pregnancies and Pearl index in studies of LNG doses other than 0.75 mg (*Continued*)

0.25 mg	699	8762	45	6.2	730.2			
0.30 mg	544	4085	23	6.8	340.4			
0.35 mg	559	3158	13	4.9	263.2			
0.40 mg	2801	25,558	75	3.5	2129.8			
Total	4631	41,802	165		3483.5	4.7	4.7	4.0 to 5.5
Larranga 1975	298	2578	14	6.5	214.8		6.5	3.6 to 11.0
Moggia 1974	314	4282 (cycles)	8	2.2	329.4	2.4	2.4	1.1 to 4.8
Schering 1978	340	3117	20	6.8	259.8	7.7	7.7	4.7 to 11.9

*Calculated assuming 13 cycles/year

The five-dose trial appeared to show a pronounced relationship between Pearl index and dose, but this finding should be interpreted with caution because the doses were not randomly assigned and no adjustments were made for potential confounders (Kesseru 1973). The trial of two doses, 0.4 mg and 0.75 mg (Canzler 1984), did not find such a relationship, and no association was evident across all six studies, or across all 15 groups of women using LNG of any dose. One report suggested that pregnancy rates were lower in subjects with higher coital frequency (and thus, with higher total drug intake) (Kesseru 1973).

Safety and acceptability

The majority of menstrual cycles in the six studies evaluating doses of LNG other than 0.75 mg were altered to some extent. The most common change was breakthrough bleeding shortening the cycle. Moggia 1974 reported that 1.3% of the participants treated with LNG 0.35 mg had low levels of hemoglobin after a long bleeding (levels of hemoglobin were not specified). Other trials did not measure hematologic indices.

The studies provided no strong evidence of a relationship between bleeding abnormalities and either dose of LNG or frequency of pill intake. Two studies that included groups of women taking tablets of different LNG doses suggested that the incidence of disturbed cycles was similar between groups (Canzler 1984; Kesseru 1973). One report stated that cycle control worsened with increased frequency of LNG dosing (Canzler 1984), but another report specifically noted no association (Echeverry 1974). In contrast, two reports mentioned an association between higher tablet intake/cycle and longer cycles (i.e., tendency towards no bleeding), but as previously noted, such an association may be spurious (Kesseru 1973; Schering 1978). One study found a decrease in bleeding irregularities with duration of use of the method, but that may have been due to early attrition of subjects who experienced these problems (Canzler 1984).

In the four studies that reported continuation statistics, between 37% and 78% of women continued the method for at least six months (Kesseru 1973; Larranga 1975; Moggia 1974; Schering 1978). Discontinuation rates due to side effects, mainly bleeding problems, ranged between 4% and 31%.

No serious adverse events were reported in the studies evaluating postcoital use of different doses of LNG. Non-menstrual side effects included nausea, dizziness, headache, nervousness, abdominal pain and weight gain; all were mild in nature, infrequent and not tabulated in most of the studies. No consistent relationship was apparent between incidence of side effects and frequency of pill intake.

Kesseru 1973 reported that all 14 pregnancies followed through the resolution resulted in birth of healthy babies. Moggia 1974 reported no ectopic pregnancies. No abnormal pregnancies or births

in other studies were reported, but it is not clear if women in these studies were followed beyond the onset of pregnancy.

The researchers of three studies had guarded opinions of the utility of the method because of low efficacy and poor cycle control (Canzler 1984; Schering 1978; Larranga 1975). However, in spite of major menstrual irregularities acceptability of the method was described as being "good" (Schering 1978), "quite" and "rather good" (Canzler 1984; Kesseru 1973), and "excellent" (Echeverry 1974).

Hormones other than LNG

Pregnancies per 100 WY in the trials that evaluated pericoital use of drugs other than LNG ranged from zero to 433.3. The highest rate was detected during the precoital use of megestrol acetate used up to 22 hours before intercourse, prompting the researchers to reduce the time interval between the pill intake and intercourse to a maximum of 14 hours. The pericoital use of several progestagens (e.g., ethynodiol diacetate, low doses of quingestanol acetate) was associated with high pregnancy rates, while use of other drugs resulted in reasonably low Pearl indices (Table 5). While most of the hormonal drugs other than LNG were not tested extensively in a large clinical trial, the postcoital use of quingestanol in doses ranging between 0.2 mg and 2 mg was evaluated in a total of 17,079 cycles in three large clinical trials (Mischler 1974; Moggia 1974; Rubio 1970). The Pearl indices ranged from zero to 168 pregnancies per 100 WY. We did not calculate a pooled pregnancy rate for all three studies because Mischler 1974 did not report the number of pregnancies. A pooled pregnancy rate for all quingestanol doses evaluated in Moggia 1974 and Rubio 1970 was 5.3 per 100 WY (95% CI 3.5 to 7.8). The use of the lowest doses of quingestanol was associated with the highest pregnancy rates.

Table 5. Number of pregnancies and Pearl index in studies of drugs other than LNG

Study	Drug	Presented in original report				Calculated by authors		Used by authors in calculating pooled rates	
		N	Cycles	Pregnancies	Pearl index	Woman-years*	Pearl index	Pearl index	95% CI
Cox 1968 (megestrol acetate)									
	4 to 22 hours precoital	4	12	4	---	0.9	433.3		
	5 to 10 hours precoital	26	468	1	---	36.0	2.8		
	4 to 14 hours precoital	17	187	0	---	14.4	0		
Mischler 1974 (by quingestanol acetate dose)									
	0.5 mg	126	518	---	36	39.8			
	0.6 mg	127	410	---	38	31.5			
	0.75 mg†	447	2388	---	23.1	183.7			
	0.75 mg†	350	1424	---	20.2	109.5			
	1.5 mg†	439	3355	---	5.4	258.1			

Table 5. Number of pregnancies and Pearl index in studies of drugs other than LNG (*Continued*)

	1.5 mg[†]	485	1532	---	0.8	117.8			
	2 mg	201	861	---	1.2	66.2			
Moggia 1974	quinges-tanol acetate	585	4732	11	2.7	364.0	3.0	3.0	1.5 to 5.4
Rubio 1970 (by quingestanol acetate dose)									
	0.2 mg	22	50	7	168	3.8	182.0	182.0	74.1 to 379.5
	0.3 mg	25	100	3	36	7.7	39.0	39.0	8.0 to 113.9
	0.4 mg	13	72	1	16.6	5.5	18.1	18.1	0.5 to 101.3
	0.5 mg	181	633	5		48.7	10.3	10.3	3.3 to 24.0
	0.8 mg	200	1004	0		77.2	0	0	0 to 4.8
Szontagh 1969	dienestrol	10	50	0		3.8	0		
	dienestrol + ethyn-odiol-diacetate	20	60	0		4.6	0		
Zanartu 1974	retropro-gestogen	127	783 (months)	39	4.5	65.3	59.8[‡]	59.8	42.5 to 81.7
	ethynodiol	15	130 (months)	7	36.9	10.8	64.6[‡]	64.6	26.1 to 133.5
	norgestrieno	72	452 (months)	7	2.6	37.7	18.6[‡]	18.6	7.5 to 38.3
	clogestone	119	465 (months)	7	2.5	38.8	18.1[‡]	18.1	7.3 to 37.2
Zanartu 1976 (by clogestone dose)									
	1.0 mg	102	649 (months)	9	17	54.1	16.6	16.6	7.6 to 31.6

Table 5. Number of pregnancies and Pearl index in studies of drugs other than LNG (*Continued*)

	1.2 mg	77	467 (months)	6	15	38.9	15.4	15.4	5.7 to 33.6
	2.0 mg	127	545 (months)	7	15	45.4	15.4	15.4	6.2 to 31.8

*Calculated assuming 13 cycles/year
†Results from the same dose are from different clinical sites; data could not be combined without the numbers of pregnancies.
‡Recalculated including pregnancies excluded from the original analysis: 36 in the retroprogestogen group, 3 in the ethynodiol group, 6 in each of the norgestrienone and clogestone groups.

Similar to the previous studies, the trials evaluating different drugs for pericoital contraception found that menstrual irregularities were the most common side effects. Several researchers noted that the postcoital regimens were well tolerated by the patients in spite of the menstrual problems (Rubio 1970; Zanartu 1974). However, Mischler 1974 concluded that the incidence of intermenstrual bleeding was "probably unacceptable" when quingestanol was used more than 12 times per cycles. The basis for this conclusion was unclear, because acceptability data were not described in the report.
Reported non-menstrual side effects included occasional gastrointestinal symptoms (e.g., dyspepsia, nausea), breast discomfort, headaches and nervousness. All these side effects were mild and almost never caused discontinuation.
None of these reports provided information on serious adverse events or pregnancy outcomes.

DISCUSSION

Different approaches to coitally-dependent oral contraception have been tested over the last 40 years. The first experience dates back to the late 1960s when estrogens were given for five to six days after sexual intercourse to prevent pregnancy (Morris 1973). Although high doses of estrogen appeared effective in preventing implantation if given in the early postovulatory period, use was associated with undesirable and potentially harmful side effects. This led to the shift of research efforts to lower repeated doses of estrogens and safer progestagens. We included in this review a brief description of the data from seven trials that evaluated pericoital repeated use of different estrogens and progestagens other than LNG for pregnancy prevention. Only one drug - quingestanol - was studied extensively. The further development of this drug was stopped, apparently due to the high rates of intermenstrual bleeding associated with frequent use of high doses of the drug, or poor efficacy associated with the use of low doses of the drug. The exploratory nature of other trials that tested pericoital use of hormones other than LNG limited our ability to make strong conclusions about contraceptive efficacy of any of these compounds.

The clinical evaluation of LNG as a progestin-only postcoital contraceptive was initiated in early 1970s. We included the reports of six studies that evaluated different doses of pericoital LNG. The major side effect reported in these trials was menstrual disturbance. In spite of the high frequency of menstrual side effects, the postcoital LNG was well tolerated by women. The studies evaluating different doses of LNG were followed by clinical testing of the 0.75 mg dose of LNG, eventually marketed as Postinor, a brand of LNG 0.75 mg, for regular postcoital contraception by women with low coital frequency. Below we discuss the results of 16 studies evaluating different doses of LNG.

Summary of main results

In the trials reviewed, pericoital use of LNG resulted in a pooled pregnancy rate of 4.9 per 100 WY (95% CI 4.3 to 5.5). If this rate applies uniformly over time, it corresponds to a life-table risk of pregnancy of 2.4% in six months, which compares favorably to the estimated six-month risk of pregnancy in women using other coital-dependent contraceptives (7.8% for male condom, 11.1% for female condom, and 15.7% for spermicides) (Taylor 2009). A commonly cited estimate of the risk of pregnancy in one year among women using no method is 85% (Trussell 2004).
The pregnancy rates for LNG varied significantly across studies (from 2.2 to 18.6 pregnancies per 100 WY). The variations in the pregnancy rates could be due to chance, differences in underlying fertility among study populations, in coital frequency and patterns of use of the method. For example, some trials of LNG included women of younger age, often with evidence of ovulatory cycle and history of pregnancy with the current partner, whereas others did not have such strict fertility requirements, and therefore could have

less fertile study populations. Reduced fertility due to postpartum lactational amenorrhea could explain lower pregnancy rates in the studies evaluating LNG doses other than 0.75 mg.

Differences in coital frequency, and correspondingly in the total LNG dose, could also influence pregnancy risk. None of the studies that evaluated doses of LNG other than 0.75 mg had limited sexual activity during the trial. The average coital frequency of six sexual acts a month in these trials, compared to four acts a month in the LNG 0.75 mg trials, could have increased the risk of conception among study participants. However, despite the higher coital frequency, these trials reported Pearl indices equal to or lower than the trials evaluating LNG 0.75 mg. Some researchers suggested that frequent use of postcoital LNG was just a different way of periodical administration of progestagens. The higher total dose of hormone ingested by such women may increase the efficacy - not an unreasonable speculation given the pharmacokinetic data on the long half life of oral LNG (He 1990).

Available data indicates that repeated pericoital LNG use was safe in the studies reviewed. Studies reported no serious side effects or adverse pregnancy outcomes. The main side effect was bleeding irregularity. Other side effects were similar to those experienced by women using other hormonal methods. Despite these side effects, most users were satisfied with the method. Proper counseling in a clinical trial setting could have contributed to the high acceptability of the method.

In conclusion, the existing data suggest that 'on demand' use of oral high-dose LNG (0.75 mg or higher) is safe and well tolerated by women. Its contraceptive efficacy compares favorably with other coitally-dependent methods of contraception. According to a 2004 survey of 1978 women conducted by the Guttmacher Institute, more than half of women aged 18 to 44 at risk of unintended pregnancy in the US reported having had sex once a week or less in the prior three months (Frost 2009). Given the high proportion of women reporting infrequent sex, the coitally-dependent oral LNG has high potential to contribute to a reduction in unintended pregnancy and abortion rates.

Quality of the evidence

We used the GRADE approach to evaluate the quality of evidence (GRADE 2004) including several key elements: study design, study quality, consistency and directness of the results. The prospective non-comparative design of most of the studies included in this review was appropriate to evaluate contraceptive efficacy of the pericoital use of hormonal contraceptives given the rarity of pregnancy outcome. Using the Pearl index rather than life-table statistics may compromise interpretation, due to the variable duration of use of the method both between and within trials. The value of Pearl index for evaluation of long-term contraceptive effectiveness is limited (Trussell 1991). However, given that the duration of follow up in most of the trials did not exceed one year, Pearl index was an adequate way of examining the efficacy data of pericoital contraception.

The varying methodological quality of the included studies was described in detail earlier in this review (Risk of bias in included studies). Briefly, some of the reports lacked details of the study, including clear treatment instructions, the inclusion criteria, the intended and the exact actual duration of follow up in calendar time, the proportion of women lost to follow up (who might have had undetected pregnancies during method use), and the trial procedures, including methods of ascertaining pregnancies. At least three trials included sizeable proportions of postpartum and lactating women, who were at minimal risk of pregnancy without any contraceptive. In many instances the listed shortcomings may have been due to inadequate reporting rather than actual quality of implementation. Several studies that provided the sizable proportion of the data for this review, were well designed, implemented and reported (He 1991; Kesseru 1973; Larranga 1975; WHO 1987; WHO 2000).

Despite some variations in the estimates of treatment effect, the pregnancy rates were reasonably low consistently across the studies. The large overall number of participants included a broad cross section of the population in terms of age and reproductive history; therefore, the results could be generalized to other populations of interest.

In general, the quality of evidence provided by observational studies is considered low. However, in our opinion, the large total amount of data from diverse populations, acceptably low pregnancy rates and the consistency of the results across studies raises the evidence grade from low to moderate.

AUTHORS' CONCLUSIONS

Implications for practice

In the studies reviewed, pericoital use of LNG was an effective, safe and acceptable method of contraception. An oral contraceptive designed to be used only at the time of intercourse has potential benefits as well as a large pool of potential users (Arowojolu 2000; Lerkiatbundit 2000; Britwum 2006). Rigorous research is needed to confirm the promising but incomplete findings. Until such data become available, compliance with the WHO recommendation that deems postcoital use of LNG unsuitable for regular contraception seems prudent (WHO 2000).

Implications for research

High-quality research is needed to confirm the efficacy and safety of a standard regimen of pericoital use of LNG as a primary means of contraception for women who have infrequent intercourse. If the method is shown to be efficacious, safe and acceptable, the existing WHO recommendations regarding the suitability of oral high-dose LNG for regular pericoital contraception could be revised, and marketing strategies could be re-evaluated.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Canzler 1984

Methods	Prospective comparative non-randomized trial. One site at the Women's Clinic of the Medical Academy of Magdeburg (Germany). Participants were followed on a quarterly basis and were given diaries to record pill intake, coital acts and bleeding. Information on other side effects was also collected through interview and questionnaires.
Participants	104 women attending the Women's Clinic of the Medical Academy of Magdeburg. Age range was 15 to 35 years in 0.4 mg group and 15 to 19 years in 0.75 mg group.
Interventions	a) LNG 0.4 mg group: one tablet within 12 hours after sexual intercourse (N=77) b) LNG 0.75 mg group: two tablets of LNG 0.25 mg right before and one tablet of LNG 0.25 mg 8 hours after sexual intercourse (total of LNG 0.75 mg per coital act) (N=27).
Outcomes	Pregnancy, side effects including bleeding problems
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	No defined term of follow up. Thus, no criteria for defining 'completeness'. In the 0.4 mg group, treatment was discontinued in almost 60% of women after an average of 9.5 cycles; in the 0.75 mg group, treatment was discontinued in 56% after average of 7.3 cycles. Lost to follow-up numbers were not reported.
Free of selective reporting?	Yes	All results corresponded to the specified outcomes.
Free of other bias?	No	Treatment assignments were not random; no information on how pregnancy outcome was ascertained; no information on how sample size was determined; no statistical methods; potential confounders were not defined although researchers reported assessment of the effect of coital frequency, time between coitus and treatment, duration of treatment, and number of tablets taken on treatment effect. The methods of this assessment were not stated.

Eligibility criteria?	Yes	To be enrolled in the study women had to be healthy, have coital frequency of up to 10 times per month and evidence of biphasic cycle.

Chernev 1995

Methods	Case series. One site at the Bulgarian Family Planning Association clinic in Sofia. Participants were followed monthly for a period of six months.
Participants	120 women of 16 to 25 years of age attending the Bulgarian Family Planning Association clinic in Sofia. All participants were either students or professionally active young women who had previously used Postinor, a specific brand of LNG 0.75 mg. Most had regular menses. None had a history of liver or venous diseases, obesity or deficient body weight. Coitus on an irregular basis.
Interventions	One pill of LNG 0.75 mg immediately (1 hour) after an unprotected intercourse over a period of 6 months; no more than 4 times a month.
Outcomes	Pregnancy, side effects including bleeding irregularities
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	No	The planned total duration of follow up was 60 woman-years (120 women x 6 months of follow up). However, only 43.8 woman-years of use of the study method were reported (73% of expected). Information on how many women were known to have discontinued method use or were lost to follow up while still using the method was not provided.
Free of selective reporting?	No	Outcomes were not pre-specified.
Free of other bias?	No	No comparison group; no information on how pregnancy outcome was ascertained; no information on how other study outcomes were ascertained; no information on how sample size was determined; no statistical methods.

Chernev 1995 (*Continued*)

Eligibility criteria?	No	

Cox 1968

Methods	Non-concurrent case series. Participants were followed for a total of 667 cycles.
Participants	47 women; unknown source for participants; characteristics unstated.
Interventions	Three groups of participants were instructed to have coitus after taking megestrol acetate 0.5 mg: first group (N=4) to have coitus between 4 and 22 hours after taking the drug; second group (N=26) to have coitus between 5 and 10 hours after taking the drug dosing; and third group (N=17) to have coitus between 4 and 14 hours after taking the drug.
Outcomes	Pregnancy, side effects
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	No	No intended duration of follow up is provided so 'completeness' of follow up cannot be assessed. No information on lost to follow up or any indicator of continuation except mean duration of use.
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy and side effects.
Free of other bias?	No	No information on how pregnancy outcome was ascertained; no information on how other study outcomes were ascertained; no description of study procedures, schedule of follow-up visits and intended duration of follow up; no information on how sample size was determined; no statistical methods; potential confounders were not defined; their effect on treatment effect was not analyzed.
Eligibility criteria?	No	No eligibility criteria were provided.

Echeverry 1974

Methods	Case series. One site at Centro Piloto de PROFAMILIA in Bogota. Participants completed diaries for pill intake, sex acts and side effects including bleeding.
Participants	127 women attending Centro Piloto de PROFAMILIA in Bogota 18 to 40 years of age; all parous; 34 (27%) were <70 days postpartum and amenorrheic at admission.
Interventions	One pill (LNG 1 mg) within 8 hours following an unprotected intercourse. In the event of successive acts one pill would suffice as long as it was taken within 8 hours of the first intercourse.
Outcomes	Pregnancy, discontinuation rate, side effects including bleeding abnormalities
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	52% of the enrolled women were reported to have dropped out of the study; more than half left after the first visit and the others left between 1 and 10 months of treatment. These women may include both participants who were known to have discontinued method use without having become pregnant and participants who were lost to follow up while still using the method.
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy, discontinuation rates and side effects.
Free of other bias?	No	No comparison group; no information on how pregnancy outcome was ascertained; no description of study procedures, schedule of follow-up visits and intended duration of follow up; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Unclear	The only two specified election criteria were voluntary selection of post-coital contraception among all of the methods offered, and no use of hormonal contraception in the previous year.

He 1991

Methods	Randomized controlled trial. Randomization was conducted according to a "random table" generated by the Shanghai Institute of Planned Parenthood Research. Participants were followed for a period of 10 weeks consisting of a pretreatment cycle, a treatment cycle and the first half of the post-treatment cycle. They were given a diary card to record basal body temperature, vaginal bleeding, acts of intercourse, days of tablet intake and side effects.
Participants	361 women attending 10 participating centers in China. The average age was about 30 years.
Interventions	One pill of Chinese- versus Hungarian-made tablet of LNG 0.75 mg taken as soon as possible after the first coitus and no later than 8 hours after. A second tablet was taken 24 hours later regardless of whether another coital exposure had occurred during that time. Subsequently, one tablet was taken after each further act of intercourse in this cycle with a maximum of one tablet per 24-hour period, irrespective of coital exposures during that period.
Outcomes	Pregnancy (as detected by measuring ß-hCG in blood), cycle control and other side effects during one month of repeated use
Notes	LNG 0.75 mg was to be used during the periovulatory period, defined as days -7 to +7 (day 0 = estimated day of ovulation based on the basal body temperature charts of the pretreatment cycle). Except for the periovulatory period, a barrier method (condom) was to be used at other times in the cycle. This study thus did not actually test the postcoital method alone. This randomized trial compared contraceptive effectiveness and safety of the Chinese- and Hungarian-made tablets. Given the purpose of this review and the fact that no significant difference was found between the two types of LNG pills, we included the overall results in the analysis.

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	A total of 153 women were excluded from the study or data analysis: 88 women were excluded during the study prior to treatment for various reasons (e.g., pregnancy, personal, medical, lost to follow up); 65 were excluded from data analysis after they received treatment due to protocol violations (erroneous recruitment or treatment) .
Free of selective reporting?	Yes	Outcomes were specified.
Free of other bias?	No	No information on how sample size was determined; no statistical methods.

He 1991 (*Continued*)

Eligibility criteria?	Yes	Included: Healthy sexually active women with regular menstruation (25 to 35 days) during the past 6 months, aged 21 to 40 years, married, have been pregnant by their present husband within the last 5 years, with no contraindication to hormonal contraception. Excluded: Women with a history of pelvic inflammatory disease since the last pregnancy, postabortion or postpartum sepsis, difficulty conceiving the last pregnancy, breastfeeding, who had used an IUD or hormonal contraception during the last 3 months, or had abnormal findings on pelvic exam.

Kesseru 1973

Methods	Prospective comparative non-randomized trial. One site at the fertility outpatient clinic of the Marcelino Research Institute in Lima, Peru. Participants were followed monthly at first and then every two months.
Participants	A total of 4631 parous women of 15 to 48 years of age attending the fertility outpatient clinic of the Marcelino Research Institute for contraceptive services. Most of the participants belonged to lower-middle socio-economic level.
Interventions	One LNG tablet immediately (but no later than 3 hours) after each sexual intercourse. Five groups: 28 women were assigned to the 0.15 mg group; 699 to the 0.25 mg group; 544 to the 0.30 mg group; 559 to the 0.35 mg group; and 2801 to the 0.40 mg group.
Outcomes	Pregnancy, menstrual cycle patterns, side effects, and reasons for discontinuation. Acceptability was ascertained by mean duration of treatment, frequency of forgotten pills and drop-out rates due to side effects.
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	Yes	Approximately 68% of the participants had more than six months of treatment and 39% more than 12 months of treatment. Early discontinuation ranged from 25% to 31%.

Kesseru 1973 (*Continued*)

Free of selective reporting?	Yes	All results presented in the article correspond to the specified outcomes.
Free of other bias?	No	No information on how pregnancy outcome was ascertained; no intended duration of follow up; no information on how sample size was determined; no description of statistical methods; potential confounders were not defined or adjusted for, but researchers commented on the apparent effect of duration of treatment, coital frequency, and number of pills taken on treatment effect.
Eligibility criteria?	Unclear	Only two eligibility criteria were specified: healthy women of childbearing age and of proven fertility (a history of at least one pregnancy). Definition of childbearing age was not provided.

Klawe 1984

Methods	Case series. Participants were followed from 5 to 11 months of use.
Participants	32 women, 35 years of age or older, parous, with no more than 4 acts of intercourse a month.
Interventions	LNG 0.75 mg: presumably one pill immediately (1 hour) after intercourse; second pill in case of another intercourse within 3 hours; third pill next morning in case of further acts of intercourse. No more than a total of four pills a month were recommended.
Outcomes	Pregnancy, side effects
Notes	Seven out of 32 women were between 41 and 45 years of age (potentially reduced fertility) .

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	Yes	No intended duration of follow up is provided so 'completeness' of follow up cannot be assessed. No information on lost to follow up or any indicator of continuation except average duration of use.
Free of selective reporting?	Unclear	Primary outcomes were not specified.

Klawe 1984 (*Continued*)

Free of other bias?	No	No comparison group; no information on how pregnancy outcome was ascertained; no description of study procedures, schedule of follow-up visits and intended duration of follow up; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Unclear	Young girls were excluded.

Kliment 1986

Methods	Case series.
Participants	40 women ages 18 to 36 years attending a gynecological clinic in Bratislava, with irregular sexual life and evidence of two-phase menstrual cycle. Participants had no bleeding disorders, normal colposcopic findings, no liver or gall-bladder diseases, did not smoke, were not obese, and were "psychically balanced."
Interventions	One LNG 0.75 mg pill immediately (within one hour) after intercourse; second pill in case of another intercourse after 3 hours; possibly a third tablet the next day.
Outcomes	Pregnancy, side effects
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	No	No information on lost to follow up or any indicator of continuation except mean and maximum duration of use.
Free of selective reporting?	No	Primary outcomes were not specified.
Free of other bias?	No	No comparison group; no description of the study procedures including frequency of follow-up visits or intended duration of follow up; no information on how pregnancy outcome or other outcomes were assessed; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	No	None stated.

Larranga 1975

Methods	Case series. Presumably one site at the Department of Obstetrics and Gynecology of University San Marcos, Lima, Peru. Participants were followed on a monthly basis for up to 16 months. They were given a card to record coitus, tablet intake, and side effects.
Participants	298 low-income, parous women of 16 to 45 years of age living in a suburb of Lima, Peru; presumably attending clinic at the Department of Obstetrics and Gynecology of University San Marcos. All had regular menstruation. At admission, 45% were using oral contraceptives, and 15% were lactating.
Interventions	One pill of LNG 1 mg immediately after each intercourse.
Outcomes	Pregnancy, bleeding problems, other side effects, discontinuation and reasons for discontinuation. Acceptability was measured as discontinuation rate by the life table method by two-month intervals.
Notes	All lost to follow-up participants were assumed to have stopped using the pills during the interval.

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	Yes	Number of women continuing and discontinuing for specified reasons presented for each month after admission. At 6 months, 60% were continuing, and 27% had been lost to follow up.
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy, discontinuation rates and reasons for discontinuation, and side effects. Discontinuation rates are referred to as acceptability rates.
Free of other bias?	No	No comparison group; method of pregnancy detection was not specified.
Eligibility criteria?	Unclear	No eligibility criteria were specified.

Mischler 1974

Methods	Prospective comparative non-randomized trial. Four sites in Mexico, Peru, Argentina and Chile. Total enrollment was 2792.
Participants	617 women of upper-middle and upper socioeconomic status in Mexico; 1340 women from upper-middle and upper and very low socioeconomic group in Peru; 350 women

Mischler 1974 (*Continued*)

	of low and very low socioeconomic status in Chile; and 485 women of middle class in Argentina.
Interventions	With one exception, all the women were instructed to take a dose of quingestanol acetate within 24 hours of every act of intercourse. Only one dose was to be taken in any 24-hour period. Modification: 300 women were instructed to take at least 3 to 4 doses of quingestanol acetate 0.8 mg in the first two weeks of each cycle whether or not they had intercourse. The range of doses of quingestanol acetate included 0.5 mg (n=243), 0.6 mg (n=127), 0.75 mg (n=797), 0.8 mg (n=500), 1.5 mg (n=924) and 2.0 mg (n=201).
Outcomes	Pregnancy, side effects
Notes	Given the purpose of this review the data from the 300 women using coital-independent treatment were not included in this analysis. Some participants are also presented in Rubio 1970; we include the overlapping data only once in this review.

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	No	No intended duration of follow up was provided so 'completeness' of follow up cannot be assessed. No information on lost to follow up or any indicator of continuation except average duration of use.
Free of selective reporting?	No	Primary outcomes were not specified. Results included pregnancy and side effects.
Free of other bias?	No	No information on how outcomes were ascertained; no description of study procedures, schedule of follow-up visits and intended duration of follow up; no information on how sample size was determined; no statistical methods; potential confounders were not defined, but the researchers commented on the apparent effect of number of pills taken per cycle as well as dose on treatment effect.
Eligibility criteria?	Yes	To be enrolled in the study women had to be fertile with a minimum of two previous pregnancies, to be willing to have another baby if the method was not successful, to have no contraindications to drug therapy, and to have an expected frequency of coitus of 2 to 4 times per week.

Moggia 1974

Methods	Prospective comparative non-randomized trial. One site at the Ramon Sarda Maternity and Children's City Hospital of Buenos Aires, Argentina. Participants were followed every 1 to 2 months and were given a calendar on which to record sex, pill intake, and bleeding.
Participants	899 women were enrolled in the trial usually upon discharge (after delivery) from the Ramon Sarda Maternity and Children's City Hospital of Buenos Aires. The women were generally of the middle socioeconomic class. Average age was 28 years. All women were parous, and a mean of 3.8 months since last pregnancy.
Interventions	Group 1: quingestanol acetate 1.5 mg (N=585). Group 2: LNG 0.35 mg (N=314) taken within 1 hour after coitus. If intercourse recurred after 3 hours, the dose had to be repeated.
Outcomes	Pregnancy, side effects including bleeding problems, discontinuation and reasons for discontinuation
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	In the quingestanol group, 69% of women completed 6 or more cycles; 12% completed 12 or more cycles; 5% completed 18 or more cycles (range 1 to 20). In the LNG group, 37% completed 6 or more cycles; 35% completed 12 or more cycles and 23% completed 18 or more cycles (range 1 to 26).
Free of selective reporting?	Yes	All outcomes were specified; all results corresponded to the pre-specified outcomes.
Free of other bias?	No	Treatment assignments were not random; no description of how sample size was determined; no information on how pregnancy was assessed; no statistical methods; no adjustment for confounding between groups.
Eligibility criteria?	No	No eligibility criteria are provided.

Nirapathpongporn

Methods	Case series. Participants were followed on a monthly basis for 10 months.
Participants	129 Thai women aged 16 to 44 attending the Population and Community Development Association in Bangkok, Thailand.
Interventions	One pill of LNG 0.75 mg immediately (1 hour) after intercourse; second pill in case of another intercourse after 3 hours; third pill next morning (or comparable time) in case of multiple acts of intercourse.
Outcomes	Pregnancy, side effects, discontinuation
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	Of 129 women: 52 (40%) completed the intended 10 months of follow up (or became pregnant), 14 (11%) discontinued early and 63 (49%) were lost to follow up.
Free of selective reporting?	Unclear	Primary outcomes were not specified (study of "safety and effectiveness"). Results included pregnancy, reasons for discontinuation, and side effects.
Free of other bias?	No	No comparison group; no information on how pregnancy outcome or other outcomes were assessed; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Yes	Healthy, sexually active but with infrequent intercourse; at least one prior pregnancy; willing to return for 10 monthly follow-up visits; had to be "interested to use Postinor [a brand of LNG 0.75 mg] as the only contraceptive during the study."

Rubio 1970

Methods	Prospective comparative non-randomized trial. Three sites in Mexico, Peru and Chile. Participants were followed for a total of 2281 cycles.
Participants	317 women of upper-middle and upper socioeconomic status in Mexico; 65 women from upper-middle and upper and very low socioeconomic group in Peru; and 135

Rubio 1970 (*Continued*)

	women of low and very low socioeconomic status in Chile. Mean age was 28 years, and mean number of previous pregnancies was more than 3.
Interventions	Participants were instructed to take a dose of quingestanol acetate within 24 hours of every act of intercourse. Only one dose was to be taken in any 24-hour period. The range of doses of quingestanol acetate included 0.2 mg (n=22), 0.3 mg (n=25), 0.4 mg (n=13) , 0.5 mg (n=221), 0.75 mg (n=36) and 0.8 mg (n=200).
Outcomes	Pregnancy, side effects, assessment of endometrial histology and cervical mucus
Notes	Some participants are also presented in Mischler 1974; we include the overlapping data only once in this review.

Risk of bias

Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	No	No intended duration of follow up; 'completeness' of follow up could not be assessed. No information on loss to follow up or any indicator of continuation except average and maximum duration of use.
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy, side effects, results of endometrial histology and cervical mucus assessment.
Free of other bias?	No	No information on how outcomes were ascertained; no description of study procedures, schedule of follow-up visits and intended duration of follow up; no information on how sample size was determined; no description of statistical methods; potential confounders were not defined or accounted for in an analysis, but researchers commented on the apparent effect of number of pills taken per cycle as well as dose of the drug on treatment effect.
Eligibility criteria?	Yes	To be enrolled in the study women had to be fertile with a minimum of two previous pregnancies, to be willing to have another baby if the method were not successful, to have no contraindications to drug therapy, and 4) to have an expected frequency of coitus of 2 to 4 times per week.

Sas

Methods	Case series. Department of Obstetrics and Gynecology in the University of Szeged Medical School, Hungary. Participants were followed for 2 to 12 months.
Participants	50 women, 16 to 39 years of age, attending clinic at the Department of Obstetrics and Gynecology in the University of Szeged Medical School, Hungary. All subjects were parous or had biphasic basal body temperature. Most subjects had stopped using oral contraceptives for side effects or other reasons and could not use intrauterine device due to side effects or other reasons.
Interventions	One pill of LNG 0.75 mg immediately (1 hour) after intercourse; second pill in case of another intercourse after 3 hours.
Outcomes	Pregnancy, side effects
Notes	37 had no previous pregnancy; potential fertility of these 37 women was assessed by curve of basal temperature that was characteristic of biphasic cycle.

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Unclear	No intended duration of follow up; 'completeness' of follow up could not be assessed. Range of duration of use was 2 to 12 months; 16% of the study participants used the method for at least 6 months. No information of loss to follow up was provided.
Free of selective reporting?	Unclear	Primary outcomes not specified.
Free of other bias?	No	No comparison group; no description of the study procedures including frequency of follow-up visits; no information on how pregnancy outcome or other outcomes were assessed; no description of study procedures, schedule of follow-up visits, or intended duration of follow up; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	No	None stated.

Schering 1978

Methods	Case series. Three clinical sites affiliated with Marcelion Institute in Lima, Peru.

Schering 1978 (*Continued*)

Participants	340 women attending three different sites in Peru affiliated with Marcelino Institute in Lima. 82% were less than 35 years old and all were parous.
Interventions	One pill of LNG 0.6 mg immediately after each intercourse.
Outcomes	Pregnancy, bleeding problems and other side effects, discontinuation rates and reasons for discontinuation. Acceptability was ascertained by frequency of forgotten pills and drop-out rates due to side effects.
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	No intended duration of follow up; 'completeness' of follow up could not be assessed. 73% of women had 6 complete months of treatment and 56% had 12 months; 43% of women discontinued early. Proportion lost to follow up was not provided.
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy, discontinuation rates and reasons for discontinuation, and side effects.
Free of other bias?	No	No comparison group; no description of the study procedures including frequency of follow-up visits; methods of ascertainment of pregnancy or other study outcomes were not specified; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	No	No eligibility criteria were specified.

Seregely 1982

Methods	Case series. 15 clinical sites in Hungary. Participants were followed monthly, and were given diaries on which to record menstrual data and coital frequency.
Participants	1315 women, 14 to 40 years of age

Seregely 1982 (*Continued*)

Interventions	One tablet of LNG 0.75 mg immediately after coitus (within 1 hour); second pill if another intercourse occurred 3 hours or later. In case of multiple acts of intercourse, 1 tablet was taken after the first act, another after 3 hours and 1 tablet on the following day.
Outcomes	Pregnancy, side effects; bleeding data via menstrual calendar; discontinuation and reasons for discontinuation.
Notes	

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	Researchers estimated drop-outs to be 15% to 20%.
Free of selective reporting?	Yes	Specified outcomes were reported; in addition researchers presented results on discontinuation and reasons for discontinuation.
Free of other bias?	No	No comparison group; methods of pregnancy ascertainment was not specified; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Yes	Inclusion: Sexually mature and gynecologically healthy women, 14 to 40 years of age, who did not want a child and had intercourse no more than 4 times per month. Exclusion: puberty, pregnancy, manifestation or history of hepatic disease and intolerance to gestagens.

Szontagh 1969

Methods	Non-concurrent case series. One site at the Dept of Ob/Gyn, University Medical School of Szeged, Hungary. Participants were followed for a total of 110 cycles.
Participants	30 fertile women. No other population characteristics were presented.
Interventions	Dienestrol (N=10) as follows: one tablet containing dienestrol 2.5 mg taken immediately after intercourse; three additional tablets taken on the following day (a total dose of 10 mg after each intercourse). Dienestrol combined with ethynodiol-diacetate (N=20) as follows: one tablet containing dienestrol 2.5 mg plus ethynodiol-diacetate 0.2 mg taken immediately after intercourse; two additional tablets taken on the following day.

Szontagh 1969 (*Continued*)

Outcomes	Pregnancy, side effects including bleeding problems	
Notes		
Risk of bias		
Item	**Authors' judgement**	**Description**
Incomplete outcome data addressed? All outcomes	Unclear	All women completed their designated follow up (5 cycles for dienestrol arm and 3 cycles for arm with dienestrol plus ethynodiol-acetate).
Free of selective reporting?	Unclear	Primary outcomes were not specified. Results included pregnancy and side effects.
Free of other bias?	No	Study procedures and follow-up schedule are not described; no information on how pregnancy outcome was assessed; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Unclear	Only one eligibility criterion (fertility) was specified.

WHO 1987

Methods	Case series. Nine clinical sites in India, Cuba, former USSR, Yugoslavia, People's Republic of China, Singapore, Hungary, Tunisia and Switzerland. Participants were followed for two (or three) pretreatment cycles; one treatment cycle and one post-treatment cycle. Follow up was conducted at four-week intervals. Participants completed charts to record basal temperature and vaginal bleeding.
Participants	259 women, aged 21 to 40 years; mean of 14 months since last pregnancy
Interventions	Instructions: one tablet of LNG 0.75 mg taken as soon as possible after the first coitus and no later than 8 hours after. A second tablet taken 24 hours later, regardless of whether another coital exposure had occurred. Subsequently, one tablet taken after each further act of intercourse in this cycle with a maximum of one tablet per 24-hour period, irrespective of coital exposures during that period.
Outcomes	Pregnancy rate as determined by Pearl Index, side effects, discontinuation rates
Notes	LNG was to be used during the periovulatory period, defined as day -4 to day +2 of cycle (day 0 = estimated day of ovulation based on temperature). Except for the periovulatory period, a barrier method (condom) was to be used at other times in the cycle. This study

WHO 1987 (*Continued*)

	thus did not actually test the postcoital method alone.

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	Out of 372 women recruited into the study only 270 received treatment; 102 were excluded during pretreatment phase for a variety of reasons, including being lost to follow up. Researchers analyzed data from 259 of 270 women who received treatment; 11 participants with protocol violations (i.e. not having met the eligibility criteria) that were identified after treatment had been received were excluded from the analysis.
Free of selective reporting?	No	Primary outcomes were not specified (study "to investigate the potential of this approach to postcoital contraception"). Pregnancy rate was specified as a study outcome measure. In addition, results included side effects, discontinuation rates and reasons for discontinuation.
Free of other bias?	No	No comparison group; no description of how sample size was determined; no information on how pregnancy, coital frequency or pill use were assessed.
Eligibility criteria?	Yes	Inclusion: age 21 to 40 years, married, of proven fertility (i.e., had been pregnant by their current husband within the last five years), history of regular menstrual cycles (25 to 36 days), in good health and sexually active. Exclusion: contraindications to hormonal contraception, breastfeeding, history of pelvic inflammatory disease since last pregnancy, postabortal or postpartum sepsis, history of IUD or hormonal contraception use during three months prior to recruitment, pregnancy less than one month before recruitment, and abnormal findings on pelvic exam.

WHO 2000

Methods	Case series. Six clinical sites: Family Planning Research Institute of Sichuan (Chengdu, People's Republic of China); National Institute of Endocrinology (Havana, Cuba); University Dept of Ob/Gyn (Ljubljana, Slovenia); National Research Institute of Fertility Control (Karachi, Pakistan); Institute of Ob/Gyn (St. Petersburg, Russia); Shanghai Institute of Planned Parenthood Research, Shanghai, People's Republic of China). Participants were followed for up to 6 consecutive months and were given diaries to record acts of intercourse, tablet intake and side effects.
Participants	295 women requesting contraception from the participating institutions' family planning clinics; mean age 33 years, mean parity 3.5; mean number of living children 1.9; 31% reported that partner was away for >= 1 week (range of 3% to 92% at the six sites).
Interventions	One LNG 0.75 mg tablet by mouth as soon as possible (but no later than one hour) after each act of intercourse. If the interval between acts was less than 3 hours, no second pill was needed. If coitus recurred more than 3 hours after taking the tablet, women were instructed to take another tablet.
Outcomes	Pregnancy rate as determined by Pearl Index, bleeding (from diary cards) and other side effects, discontinuation rates and acceptability.
Notes	Final analysis was performed on an intent-to-treat basis, although 24% had protocol violations (frequency of coitus and prior contraceptive use).

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	About one-third of the enrolled participants dropped out before finishing 6 months of use, including 4.4% lost to follow up.
Free of selective reporting?	Yes	All outcomes were specified; results corresponded to the specified outcomes.
Free of other bias?	No	No comparison group; no description of how sample size was determined; no information on how pregnancy was assessed.
Eligibility criteria?	Yes	Inclusion criteria: older than legal age of consent, have regular menstrual cycles (25 to 35 days), proven fertility with their present partner, no contraindications to hormonal contraception, with a customary frequency of 1 to 4 sexual acts per month. Exclusion criteria: no pregnancy or hormonal contraception use within the past 3 months; no IUD use within the last 30

WHO 2000 (*Continued*)

		days.

Zanartu 1974

Methods	Prospective comparative non-randomized trial. Presumably one site in Santiago, Chile. Participants were followed every three months. Women were given calendars to record vaginal bleeding.
Participants	1805 women between 18 and 41 years old from the northern section of the city of Santiago attending the Unit for Fertility and Sterility Research within the Center for Study of Reproductive Biology (Dept of Ob/Gyn, University of Chile Medical School).
Interventions	One study group consisted of 333 women who took one of four progestagens before or after coitus: a) 127 women took retroprogestogen 30 mg to 40 mg; b) 119 women took clogestone 1.0 mg; c) 72 women took norgestrienone 0.5 mg, and d) 15 women took ethynodiol 0.5 mg. Women in Group 2 were followed every 3 months for pregnancy and side effects. For 1510 of 1830 total months, women were advised to take the medications no later than 6 hours before coitus. For 320 months, women were advised to take the medications immediately before or after coitus. The other group consisted of 1472 women who took one of the same 4 progestagens daily except during menses.
Outcomes	Pregnancy, side effects
Notes	The data for the women taking clogestone 1.0 mg at least 5 to 6 hours before intercourse (n=99) may overlap with Zanartu 1976, in which 102 women had the same regimen of clogestone 1.0 mg. This report does not consider the group taking the daily pills.

Risk of bias

Item	Authors' judgement	Description
Incomplete outcome data addressed? All outcomes	Yes	No intended duration of follow up; 'completeness' of follow up could not be assessed. No information on loss to follow up or any indicator of continuation except average duration of use.
Free of selective reporting?	No	Primary outcomes were not specified. Results included pregnancy, pregnancy rates after discontinuation of the method, side effects and effects on reproductive tract parameters (endometrial histology, cervical mucus, vaginal cytology).
Free of other bias?	No	No information on how pregnancy was ascertained; no information on how sample size was determined; no description of

Zanartu 1974 (*Continued*)

		statistical methods. Potential confounders were not defined, and their effect on treatment outcome was not analyzed. Researchers' Pearl Index calculation included only pregnancies resulting from method failure, i.e., pregnancies occurring while the contraceptive regimens were followed in accordance with instructions. Other women are reported as both 'unintended pregnancies' and 'drop outs'; we assume the former is accurate.
Eligibility criteria?	Unclear	Only one admission criterion was specified: a coital incidence not higher than 3 days per week.

Zanartu 1976

Methods	Prospective comparative non-randomized trial. Presumably one site in Santiago, Chile. Participants were followed every 3 months. They were given menstrual calendars to record uterine bleeding.
Participants	756 women of 19 to 45 years old of rather low socioeconomic and educational level attending the Unit for Fertility and Sterility Research within the Center for Study of Reproductive Biology (Dept of Ob/Gyn, University of Chile Medical School).
Interventions	One study group included 306 women who used clogestone, a progestagen, on the day of coitus only, following one of three regimens: a) a clogestone 1.0 mg tablet at least 5 to 6 hours prior to intercourse (n=102); or b) two clogestone 0.6 mg tablets (a total dose of 1.2 mg), one immediately before and one right after coitus (n=77); or c) two clogestone 1.0 mg tablets (a total dose of 2 mg), one immediately before and one right after coitus (n=127). Another group consisted of 450 women treated with the same progestagen daily except menses.
Outcomes	Pregnancy, discontinuation, reasons for discontinuation, return of fertility and changes in reproductive tract parameters
Notes	The data for the women taking clogestone 1.0 mg at least 5 to 6 hours before intercourse (n=102) may overlap with Zanartu 1974, in which 99 women reportedly took clogestone 1.0 mg in the same regimen. This report does not consider the group taking the daily pills.

Risk of bias

Item	Authors' judgement	Description

Zanartu 1976 (*Continued*)

Incomplete outcome data addressed? All outcomes	Yes	No intended duration of follow up was provided. 17% of study participants were known to have discontinued method without pregnancy; 9% were lost to follow up, but without information on the time duration over which these events happened, interpretation of these statistics is limited.
Free of selective reporting?	Yes	All outcomes were specified; results corresponded to the specified outcomes.
Free of other bias?	No	No information on how pregnancy was ascertained; no information on how sample size was determined; no information on frequency of coital intercourse or pill intake; no information on how sample size was determined; no statistical methods.
Eligibility criteria?	Unclear	Only one admission criterion was specified: women had to have no more than three acts of intercourse per week (in the group using clogestone coitally).

Characteristics of excluded studies *[ordered by study ID]*

Czekanowski	Information is insufficient to evaluate the quality of the study and analyze the results.
Hetenyi 1988	No information on regimen and dosage of the treatment drug
Hurtado 1975	Information is insufficient to evaluate the quality of the study and analyze the results.
Krymskaya 1983	No information on time of follow up
Kulakov 1983	No information on regimen and dosage of the treatment drug
Orley	No information on pregnancy outcome
Serov 1983	No information on time of follow up
Szczurowicz	No information on regimen and dosage of the treatment drug
Unzeitig 1989	No information on regimen and dosage of the treatment drug
Vasilev 1983	Poor quality of original publication (in Bulgarian), including unclear description of regimen

DATA AND ANALYSES

This review has no analyses.

WHAT'S NEW

Last assessed as up-to-date: 9 February 2009.

14 April 2010	Amended	typo

HISTORY

Protocol first published: Issue 1, 2009

Review first published: Issue 1, 2010

CONTRIBUTIONS OF AUTHORS

V Halpern developed the idea and registered the title. V Halpern identified the eligible reports and performed the primary data abstraction. E Raymond confirmed the reports' eligibility, performed the second data abstraction and verified the results and conclusions. L Lopez performed the second data abstraction for the characteristics of included and excluded studies and assessment of risk of bias in the included reports. E Raymond and L Lopez provided analytical and editorial input.

DECLARATIONS OF INTEREST

We have no conflict of interests to declare.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Child Health and Human Development, USA.
- Hewlett Foundation, USA.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Title was changed to include immediate precoital use: 'Repeated use of pre- and postcoital hormonal contraception for prevention of pregnancy.' Protocol title had been 'Repeated use of postcoital hormonal contraception for prevention of pregnancy.'

INDEX TERMS

Medical Subject Headings (MeSH)

*Coitus; Contraceptives, Oral, Hormonal [*administration & dosage; adverse effects]; Contraceptives, Postcoital [*administration & dosage; adverse effects]; Levonorgestrel [*administration & dosage; adverse effects]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans